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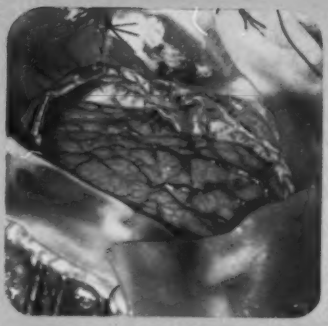

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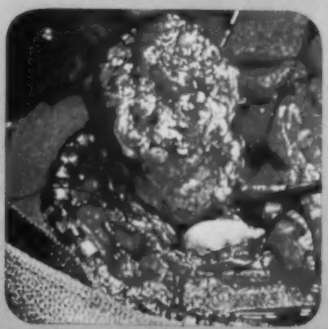

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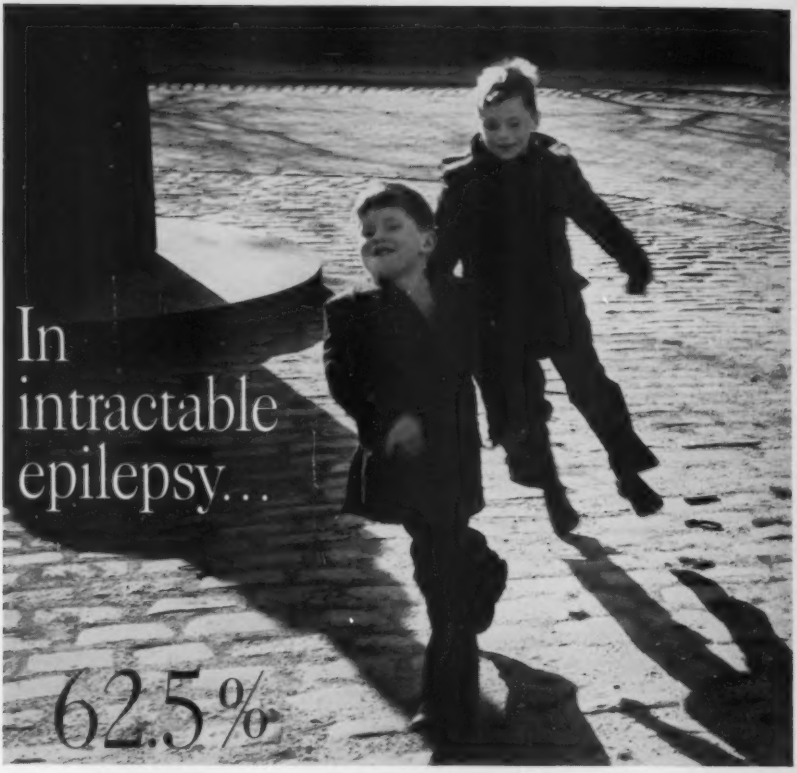

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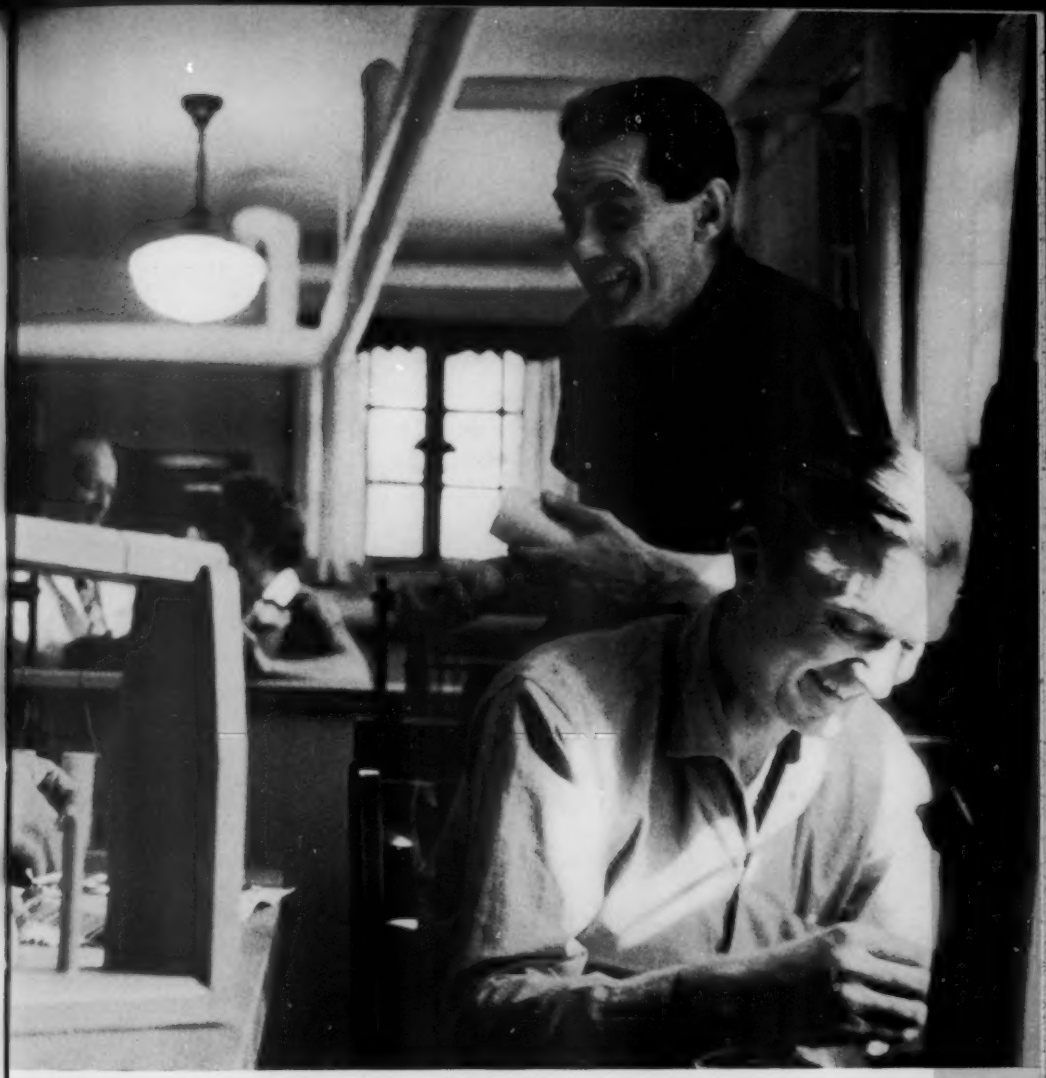

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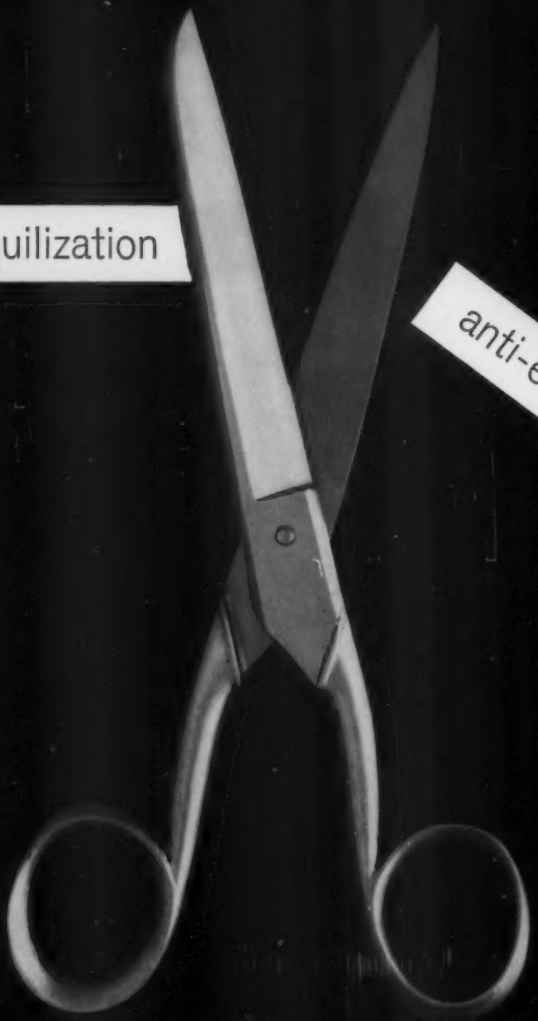

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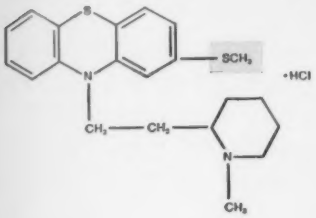

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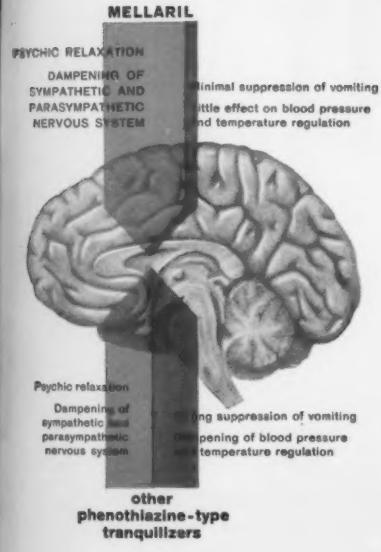

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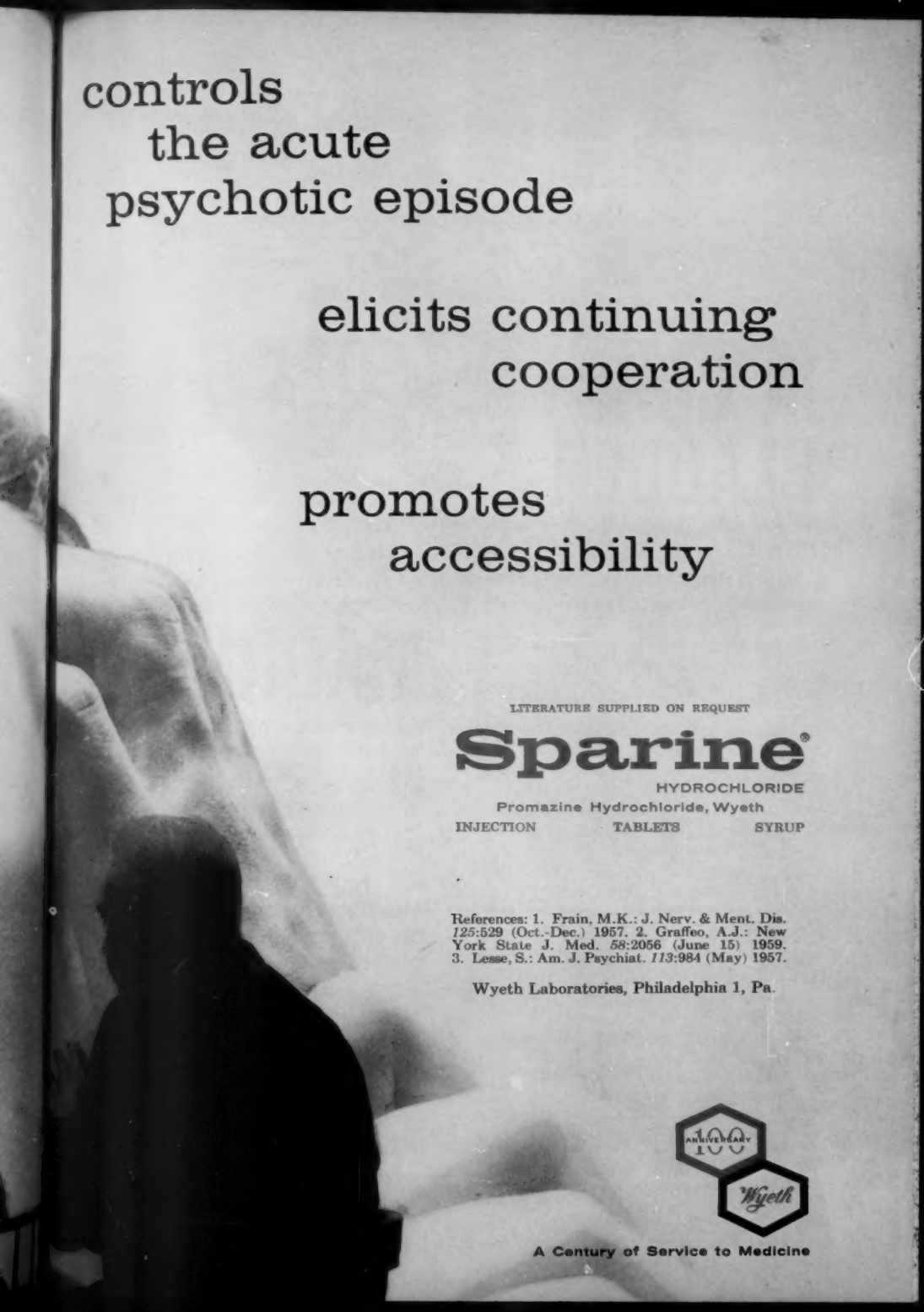

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Neurology Volume 9 • Number 12

Degenerative cerebellar ataxias

Joe R. Brown, M.D.

DESCRIPTIONS OF various families with genetic cerebellar ataxias are of undoubted value. Unfortunately, the ataxic patient arriving in the neurologist's office often fails to reveal a positive family history and frequently does not fall into any of the classic syndromes that have been described. This study reviews the etiologic data, the symptoms, and the signs in the 103 patients with degenerative cerebellar ataxia seen at the Mayo Clinic during 1957. The term "degenerative" is intended to include cerebellar ataxias of genetic origin as well as those of uncertain or undetermined cause. Excluded were patients with convincing evidence of tumors, multiple sclerosis, encephalitis, or other specific disease.

The method of the study consisted of abstracting information concerning pertinent symptoms, signs, tests, and general disease from the patient's clinical record. This information was scrutinized for similarities and differences without submitting it to formalized statistical methods.

In evaluating the symptoms, a reasonable temporal relationship was required in order to consider a particular symptom as possibly significant to the ataxic illness. Symptoms and signs due to obvious cause, those not temporally related, or those common for the age of the patient were excluded as not significant. Specifically excluded on the latter basis were minor diminution of hearing beyond the age of 55, minor impairment of vibratory sense in the lower extremities after the age of 60, and mild loss of memory or absence of abdominal reflexes beyond the age of 65. These exclusions were set arbitrarily and were based on the author's personal opinion that the findings mentioned were, in general, too common at those ages to be useful as evidence.

A study of the phenomena observed in these patients revealed certain similarities and differences which fell naturally into 3 reasonably distinct categories. It was noted that the status of the muscle-stretch reflexes acted as an indicator for each category. This permitted the simple classification of the degenerative cerebellar ataxias into normoreflexic, hyporeflexic, and hyperreflexic forms. The characteristics of each of these forms will be described in detail later. Some characteristics were common to the group of 103 patients as a whole. These characteristics will be described first, because there were few *qualitative* differences between the 3 forms in reference to these particular characteristics.

VITAL STATISTICS

The average age of the 103 patients was 49.3 years, while the ages ranged from 3 to 82 years. There were 19 patients in the age group 0 to 19 years and 51 in the age group 50 to 69. Thus, almost 70% of the patients were represented in these 4 decades, while

From the Mayo Clinic and Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.
Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 1959.

only 30% were in the other 5 decades represented. Thus, incidence reached a peak in the first 2 decades and a greater peak in the sixth and seventh decades and declined in the middle and final decades.

From point of view of age at onset, the same peaks were noted. Onset occurred in the age group 0 to 19 years in 25 patients and in the age group 50 to 69 in 51 patients. The range of age at onset extended from that implied by the statement that the disease had "always" been present to 81 years. In 8 patients, the disorder was noticed before 2 years of age. One of these patients was seen at the age of 41 and, despite slow progression of ataxia throughout the years, was still able to walk. All of this group in whom onset occurred very early had progressive ataxia, although, in some, the progression was indolent.

In the total group, 65 were males and 38 were females. However, of those less than 20 years old, 8 were males and 11 were females. In the remainder, males predominated 2:1.

The duration of the ataxia ranged from one month to forty-one years, with an average of five and one-half years. However, the average was weighted by a few patients who had been ataxic for a long length of time. The duration of illness was three years in 19 patients, less than three years in 40, and more than three years in 44 patients. Thus, the median duration of three years seems more significant than the average of five and one-half years. The average age of those who had been ataxic more than three years was not significantly different from the average age of those who had been ill less than three years. The group with more than three years' duration of the disease contained a somewhat larger number of patients with mild ataxia than did the group with short duration of illness.

ETIOLOGIC CONSIDERATIONS

Of the 103 patients, 12 revealed a history of an identical illness in other members of the family. A history of pes cavus in the families of 3 patients suggested significant genetic cause. Seven patients had a history of some indeterminate but apparently unrelated neurologic disorder. In an additional 12 patients, there was history of identified but unrelated neurologic disease, such as migraine, epilepsy, or brain tumor.

None of the patients gave a history of injury or infection that seemed pertinent.

Inquiry for possible metabolic or endotoxic causes revealed one each of the following: lipid-storage disease, carcinoma of the bronchus, carcinoma of the breast with metastasis to the liver, carcinoma of the tongue, carcinoid adenoma of the bronchus, diabetes, and gout. Instances of possible exotoxic causes included 8 patients with excessive alcoholic intake, 1 patient who used diphenylhydantoin (Dilantin), and 1 who was exposed to grain sprays. Aging as a possible etiologic factor is reflected by the fact that 34 patients had the onset after the age of 60. A number of patients had two possible etiologic factors. For example, 3 patients who admitted excessive use of alcohol revealed a history of identical ataxic illness in their family. Two patients with onset of ataxia after the age of 60 also had a history of the overuse of alcohol.

Associated somatic deformities of pes cavus, scoliosis, or both were seen in 7 patients. One patient had an abnormal electrocardiogram of the type seen in Friedreich's ataxia. This does not reflect the incidence of such abnormalities, because few patients in this group had electrocardiograms made. One patient with ataxia had myotonia and cataracts, and 1 had telangiectasis of the cornea.

Except for those patients with clear-cut evidence of identical disease or associated somatic deformity in other members of the family, the cause seems either uncertain or undetermined.

ATAXIC SYMPTOMS AND SIGNS

The "typical" patient with cerebellar ataxia would be a man of about 50 years of age who said that he had noticed the insidious onset of unsteady gait and a sense of poor balance three years previously. These symptoms would have been more pronounced when he first stood up and started to walk, when he turned quickly, or when he walked downstairs or on uneven ground. Emotional stress or the ingestion of alcohol would have increased the unsteadiness, but walking in the dark would have had little effect. During this same time, this patient would have noticed a sensation of

general weakness and fatigue, especially in the legs. These symptoms would have progressed slowly and become more constant with the passage of time. About one year previously, he would have become aware that his hands were rather clumsy when doing skilled work and that his handwriting was impaired. On direct questioning, he would admit that he had noticed that his speech had been slightly slurred and tremor of the upper extremities had occurred during the previous six months.

A review of the records of the 103 patients showed that there were symptoms of unsteady gait in 100, impaired coordination of the limbs in 70, impaired handwriting in 56, and a sense of weakness, especially in the legs, in 51 (Table 1). Speech difficulty was noticed by 40 patients. A few patients did not fit this general pattern of symptom development and will be described separately in the section on special forms of cerebellar ataxia.

The signs of cerebellar ataxia are listed in Table 2 in order of frequency. Hypotonia was the least frequently recorded phenomenon, which may be due to negligence in reporting it adequately on the neurologic record form. However, in a number of patients, hypotonia of the limbs was observed when the patient was sitting or lying, but hypertonia became prominent when he was standing or walking.

Most patients with tremor had both a static and a terminal crescendo tremor. However, in 21, the tremor was most pronounced in static postures, while the terminal crescendo tremor was most prominent in 35. An irregularly intermittent dysarthria was the most common speech difficulty observed. Modifications of this condition in some patients will be discussed later. Station was impaired in more than half of the patients, and the impairment tended to increase only mildly with the eyes closed. In testing for coordination of the limbs, impairment of the alternate motion rate and knee-pat tests was most readily observed. However, the reaction to other tests, such as finger-nose and heel-knee tests, was impaired with equal frequency. Ataxia was present slightly more often in the lower than in the upper extremities.

One patient did not have an impaired gait, and, in a few others, the limb ataxia was more marked than the gait ataxia. These few patients will be described later. In all of the remaining 98 patients, gait ataxia was the most prominent sign. In the more severely affected patients, the gait was wide-based, stiff-legged, and staggering. With milder involvement, the straight-away gait was normal, the unsteadiness appearing only when the patient started to walk or when he turned. In some patients, the ataxia was brought out only with tandem walking. Of the 103 patients, 25 demonstrated little or no limb ataxia and mild gait ataxia; 43 had mild limb ataxia and moderate gait ataxia; while 35 had severe ataxia.

NONCEREBELLAR SYMPTOMS AND SIGNS

In only 12 patients was there a pure cerebellar syndrome. The remaining 91 patients also had signs of involvement of other neurologic systems. The symptoms and signs of noncerebellar involvement were grouped in relation to 3 anatomic headings: cranial nerves and brain stem, cerebrum and pyramidal tracts, and spinal cord and peripheral nerves.

Cranial nerves and brain stem. A sense of visual blurring was a complaint in 12 patients (Table 1), while 1 specifically described his

TABLE 1
SYMPTOMS IN 103 CASES OF CEREBELLAR ATAXIA

Symptom	*Cases*
Gait unsteady	100
Impaired coordination of limbs	70
Handwriting impaired	56
Weakness	51
Speech difficulty	40
Visual blur	12
Diplopia	12
Visual loss	3
Paresthesia	27
Pain	17
Cramp	12
Sphincter dysfunction	12
Sexual impotence	8
Loss of hearing	11
Tinnitus	4
Vertigo	10
Giddiness	15
Mental change	20
Headache	17
Vomiting	6
Involuntary movements	5
Convulsion	2
Difficulty in swallowing	9
Impaired sense of smell	4
Impaired sense of taste	2

TABLE 2
SIGNS OF CEREBELLAR ATAXIA

Sign	Normo-reflexes	Hypo-reflexes	Hyper-reflexes	Total
Total cases	30	29	44	103
Ataxia				
Gait	30	29	43	102
Lower extremities	23	24	37	84
Upper extremities	20	20	32	72
Station impaired	13	20	25	58
Speech difficulty	9	14	28	51
Terminal tremor	8	12	15	35
Static tremor	6	7	8	21
Hypotonia	4	8	5	17

vision as "jiggly." Double vision was noted on one occasion by 3 patients, on a few occasions by 3 patients, on repeated variable brief occasions by 5 patients, and continuously by 1 patient. Excluding the patients with cataracts or glaucoma, visual loss was a symptom of 3 patients. Diminution of hearing was mentioned by 11 patients who were less than 55 years of age, and tinnitus was present in 4. Occasional whirling vertigo was described by 10 patients, while 15 more complained of a sense of giddiness, especially when on their feet. In response to direct questioning, 9 admitted some difficulty in swallowing; 4 noted loss of sense of smell; and 2 described impaired taste.

Nystagmus was the most frequent sign related to the cranial nerves and brain stem, occurring in 22 patients and generally being graded as of moderate degree (Table 3). In 16 instances, it was brought out on horizontal gaze, while in 6 it also had vertical components. In none was the nystagmus present in the primary position.

Next in frequency were other disorders of ocular movements which occurred in 18 patients. These included strabismus in 1 patient, third nerve palsy in 3, internuclear ophthalmoplegia in 1, and paresis of conjugate gaze, which was horizontal in 3, vertical in 1, and all directions in 1. Other abnormalities of ocular movements were described as ataxic in 3 patients, dystonic in 1, rigid in 1, and reluctant in 1. Ptosis was present in 4 patients and loss of light reflex in 1. Some patients experienced more than one disorder of ocular movements.

TABLE 3
SIGNS OF INVOLVEMENT OF CRANIAL NERVES AND BRAIN STEM

Sign	Normo-reflexes	Hypo-reflexes	Hyper-reflexes	Total
Total cases	30	29	44	103
Nystagmus	3	8	11	22
Disorders of ocular movements	3	5	10	18
Optic atrophy	2	1	2	5
Disorders of acoustic nerve	4	6	2	12
Disorders of olfactory nerve	3	1	1	5
Myoclonus	2	2	0	4
Atypical spike wave	2	1	0	3

Optic atrophy was present in 5 patients who varied in age from 8 to 59 years.

Significant diminution of hearing occurred in 12 patients who were under 55 years of age. In 1 of these, the hearing loss was hereditary. In another patient, the hearing loss was complete and associated with no response on the caloric test. In the other 23 instances in which caloric responses were tested, they were normal. Sense of smell was absent in 5 instances.

Synchronous and asychronous myoclonus was observed in 4 patients, all of whom also had terminal crescendo tremors. Three of these patients had atypical spike-wave patterns on the electroencephalogram. Electroencephalographic studies carried out on 47 patients revealed normal, nonspecific, or unrelated findings in 44.

Cerebrum and pyramidal tract. Mental symptoms were present in 20 patients less than 65 years old. In most instances, these took the form of mild forgetfulness. In 6 cases, intellectual faculties were definitely impaired. Insomnia, depression, and involuntary crying each occurred once. Headache bearing a reasonable temporal relationship to the ataxia occurred in 17 patients, while 6 complained of some nausea and vomiting. Convulsions occurred in 1 ataxic patient with a history of alcoholic abuse and in 3 patients with myoclonus. Involuntary movements complained of included withdrawal spasms in 8, tremor in 6, choreoathetosis in 2, and myoclonus in 2.

Signs of involvement of the corticospinal tract are listed in Table 4. Attention is called to Table 5 for the incidence of objective mental changes—parkinsonian rigidity, rest tremor, and choreoathetosis.

Pneumoencephalographic examinations performed in 28 patients were normal in 16. Ab-

TABLE 4
SIGNS REFERABLE TO THE PYRAMIDAL TRACT

Sign	Normo-reflexes	Hypo-reflexes	Hyper-reflexes	Total
Total cases	30	29	44	103
Babinski's sign	4	13	24	41
Abdominal reflexes abnormal	2	11	25	38
Hypertonia	1	5	13	19
Spastic paresis	0	1	10	11

TABLE 5
CEREBRAL SIGNS

Sign	Normo-reflexes	Hypo-reflexes	Hyper-reflexes	Total
Total cases	30	29	44	103
Objective mental changes	6	5	11	22
Rigidity	1	0	5	6
Rest tremor	0	0	2	2
Choreoathetosis	0	2	0	2

normal findings included evidence of dilated ventricles in 5, cerebral atrophy in 2, cerebellar atrophy in 3, and combined cerebral-cerebellar atrophy in 2.

Spinal cord and peripheral nerves. The most common symptom referable to this system was paresthesia, which was described by 27 patients (Table 1). The lower limbs were the site of the paresthesia in 21 cases, and all 4 limbs were involved in 6 patients. The paresthesia was chiefly distal in location and was most frequently described as a numbness. Tingling, a feeling of pins and needles, crawling, coldness, heat, and a sense of walking on air were also described.

Seventeen patients complained of pains that seemed related to their ataxic illness. The pains were located in the neck, the lower part of the back, and, most frequently, the legs. The quality of the pains included aches in the back or extremities, sharp pains in the extremities, and flashes of pain anywhere in the body. Painful muscle cramps were present chiefly in the lower extremities. A reduction in sexual potency was a symptom in 8 patients less than 65 years old, and urinary control proved difficult in 12 patients under 65 years of age.

Table 6 gives the incidence of significant reduction in vibratory and joint sensibility, which was usually limited to the lower limbs. The impaired sense of pain, temperature, and touch was mild and peripheral in location and usually occurred only in the lower extremities. The muscle weakness referred to in this table was distally located and usually limited to the legs.

Electromyographic examinations were normal in 6 of 14 patients. In 2 instances, there was evidence of denervation with normal conduction velocities of peripheral nerves. This was interpreted as an indication of disease of the anterior horn cells. In 2 patients with evidence of denervation, the conduction velocities were significantly reduced, a finding diagnostic of peripheral neuropathy. The conduction velocities were indeterminate in 2 patients showing denervation. One patient had low-amplitude, short-duration motor-unit potentials in a few muscles, a finding that raised the question of possible myopathy. One patient with ataxia and cataracts demonstrated a myotonic response on the electromyogram. It seems probable that an increased incidence of abnormalities of the motor unit would be found if more ataxic patients, especially those with distal weakness or hypesthesia, were examined electromyographically.

Examination of the spinal fluid was normal in 25 of 40 patients. The total protein content was from 50 to 99 mg. per 100 cc. in 12 patients, and more than 100 mg. in 3 patients. The highest value was 240 mg. One patient, age 7 years, with a pure cerebellar syndrome of one month's duration, had spinal fluid findings as follows: protein, 80 mg.; lymphocytes, 25 per cubic millimeter; and colloidal gold curve, first zone rise. Another patient, age 65, with cerebellar ataxia, hyperreflexia, and positive Babinski signs, had spinal fluid findings as

TABLE 6
SIGNS OF INVOLVEMENT OF SPINAL CORD AND PERIPHERAL NERVES

Sign	Normo-reflexes	Hypo-reflexes	Hyper-reflexes	Total
Total cases	30	29	44	103
Reduction in vibratory sensibility	3	18	14	35
Reduction in joint sensibility	1	13	13	27
Distal paresis	0	13	1	14
Impaired touch-pain-temperature sense	0	6	3	9
Electromyographic changes	0	6	2	8
Pes cavus	1	5	1	7
Scoliosis	0	4	2	6

follows: protein, 80 mg.; lymphocytes, 0; and colloidal gold curve, first zone rise. Of the 103 patients, 4 had undergone myelographic examination with negative findings except for cervical ridging which was found in 1.

CLASSIFICATION OF DEGENERATIVE CEREBELLAR ATAXIAS

As noted earlier in this paper, the status of the muscle-stretch reflexes is a simple and useful indicator in classifying the degenerative cerebellar ataxias into 3 forms: normoreflexic, hyporeflexic, and hyperreflexic. There is little difference between the 3 forms as far as the ataxic signs are concerned. However, the hyporeflexic form is characterized by a predominance of signs referable to the spinal cord and peripheral nerves, while the hyperreflexic form has a predominance of signs referable to the cerebrum and pyramidal tracts. The normoreflexic form is characterized by a minimum of signs other than cerebellar. To reduce the number of variables studied, the neurologic signs were grouped on the basis of the anatomic structure that they probably represented.

Reduction of vibratory or joint sensation was taken as evidence of involvement of the posterior columns. Muscle weakness, especially when located distally and when associated with appropriate electromyographic findings, was used as evidence of damage to the anterior horn cells. Distal reduction of pain, touch, and temperature sense or reduced conduction velocity of peripheral nerves was interpreted as evidence of peripheral neuropathy. Because these symptoms tended to occur in the same patient, peripheral neuropathy, damage to the anterior horn cells, and damage to the posterior columns formed a grouping of spinal cord-peripheral nerve involvement.

Involvement of the pyramidal (corticospinal) tracts is considered separately because it may be of either cerebral or spinal origin. Despite the objections to the use of the phrase "pyramidal signs," it is useful until more accurate terminology is developed. Absent abdominal reflexes, extensor Babinski responses, spasticity, and spastic paresis were used as evidence of involvement of the pyramidal tract. Hyperreflexia was excluded from consideration because it had been used in classifying the ataxic patients.

Cerebral involvement was indicated by signs of reduced intellectual faculties or extrapyramidal signs. Included in the latter were rigidity, immobility, alternating rest tremor, and choreoathetosis.

Signs referable to the cranial nerves and brain stem included evidence of ocular involvement, reduced function of the eighth nerve, loss of sense of smell, and myoclonus.

Normoreflexic cerebellar ataxia. Thirty patients comprised this group, which was characterized by relatively pure cerebellar ataxia and minimal noncerebellar signs (Table 7). Ten patients in this group had no noncerebellar signs. Signs referable to the posterior columns and pyramidal tracts were mild in all instances. The cerebellar signs and symptoms followed the pattern described earlier in this paper.

Hyporeflexic cerebellar ataxia. Muscle-stretch reflexes were markedly reduced or absent in the 29 patients in this group. In some instances, only the gastrocnemius reflexes were abnormal, but, in most patients, hyporeflexia was generalized. There was some increased incidence of hypotonia and impaired station, but the ataxic signs followed the general pattern described previously. Complaints of weakness were somewhat increased. Most characteristic of the hyporeflexic group was the considerable increase in signs referable to the spinal cord and peripheral nerves, as noted in Table 6. These signs were also considerably more severe than those occurring in the normoreflexic and hyperreflexic groups. Electromyographic abnormalities were most frequent in the hyporeflexic patients. The great majority of the patients with pes cavus and scoliosis were in the hyporeflexic group (Table 6).

TABLE 7
NONCEREBELLAR NEUROLOGIC SIGNS

Noncerebellar signs	*Normo-reflexes*	*Hypo-reflexes*	*Hyper-reflexes*	*Total*
Total cases	30	29	44	103
Signs referable to:				
Posterior column	3	9	18	30
Motor neuron	0	14	1	15
Peripheral nerves	0	5	3	8
Pyramidal tract	9	21	35	65
Mental changes	8	5	11	24
Extrapyramidal tract	1	2	5	8
Ocular nerve	5	11	18	34
Eighth nerve	4	6	2	12
First nerve	3	1	1	5
Myoclonus	2	2	0	4

Hyperreflexic cerebellar ataxia. Forty-four patients comprised this group in which pyramidal and extrapyramidal signs predominated. The incidence of impaired speech was increased. It was not possible from the records to accurately delineate the dysarthria observed. However, similar patients have been observed subsequently but not in this series. Some of such patients showed the more constant dysarthria of pseudobulbar origin, while others demonstrated reduced phonatory volume of parkinsonism combined with the irregularly intermittent dysarthria of cerebellar speech.

Although a moderate number of these patients had signs referable to the spinal cord, these signs were generally mild. A few had somewhat more pronounced posterior-column signs. Pyramidal signs were prominent in both frequecny and relative severity. Extrapyramidal signs were similarly prominent (Tables 4, 5, and 7). No patients with a history of overuse of alcohol were seen in the hyperreflexic group. Patients in this group had some increased symptoms of impaired speech, pains, sexual impotence, and leg cramps.

Special forms of ataxia. The great majority of patients fit the general pattern of cerebellar ataxia described in the early portion of this paper. Two syndromes, however, specifically differed from this pattern.

The first syndrome consisted of the early onset of progressive ataxia of the limbs with marked terminal crescendo tremor. Gait ataxia developed late and remained less severe than the limb ataxia. There were no other neurologic signs. This syndrome was seen in 2 patients, and the onset occurred during adult life. The syndrome was discussed by Hunt under the title of "dyssynergia cerebellaris progressiva" and is considered to be due to atrophy of the dentate nucleus.

A second special syndrome was seen in 3 children. In this syndrome, also, the ataxic signs were more intense in the limbs, and terminal crescendo tremor was prominent. Added to this syndrome, however, were synchronous and asynchronous myoclonic jerks, convulsions, and an atypical spike-wave pattern on the electroencephalogram. Mental deterioration was present in all 3 patients with this syndrome. One patient had extensor Babinski signs, while another had nystagmus and ataxic eye movements. There was no family history of a similar illness.

One patient had hyperreflexic cerebellar ataxia in association with myotonia and cataracts. His father had an identical illness.

One patient with hyperreflexic cerebellar ataxia also had anosmia, complete loss of hearing, no caloric responses, and pupils that were nonreactive to light.

Cerebellar ataxia in children. The information on the 25 patients with the onset of ataxia before the age of 20 was reviewed to see whether they differed from the adult group. The general pattern of the ataxias was the same. One special form in children is described in the preceding section. One-half of the children were classified as having severe ataxia, while only a third of the adults were so classified. The relative incidence of the hyporeflexic form was greater than in the adult group. Finally, it is of especial note that all ataxic patients with pes cavus or scoliosis had the onset of ataxia in childhood.

SUMMARY

Among 103 patients with degenerative cerebellar ataxia, incidence reached a peak in the age group 0 to 19 years and a greater peak in the age group 50 to 69. In the adult group, males predominated 2:1. Duration of the ataxia ranged from one month to forty-one years, with a median of three years.

Only 15 patients revealed a history of an identical or related condition in other members of the family. In most patients, the cause was either uncertain or undetermined.

In most patients, ataxic gait preceded and was more pronounced than limb ataxia. The group was classified into normoreflexic, hyporeflexic, and hyperreflexic forms. Patients with normoreflexic cerebellar ataxia had a paucity of other neurologic signs. In the hyporeflexic form, signs referable to the spinal cord and peripheral nerves were prominent, as were pes cavus and scoliosis. The hyperreflexic form demonstrated a predominance of pyramidal and extrapyramidal signs. Cranial-nerve, brain stem, and mental signs occurred in the 3 forms of ataxia with approximately equal frequency.

In 2 exceptional syndromes, limb ataxia was more prominent than gait ataxia.

A case of atonic cerebral diplegia with lissencephaly

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ATONIC CEREBRAL diplegia, a neglected aspect of cerebral palsy, has been estimated to affect 5 to 10% of institutionalized patients with cerebral palsy.[18,20] The clinical picture comprises flaccid weakness with marked delay in or absence of sitting and walking, severe mental defect, and deficient or absent speech. Frequently associated are convulsive disorder and microcephaly.[2,3,8,9] This syndrome has been reported in association with congenital heart disease.[5]

No description has been made of the autopsy findings in classic instances of atonic cerebral diplegia,[14] although Yannet[18] has referred briefly to deficit of ganglion cells in the cerebrum and cerebellum and Foerster[8] made passing reference to the findings in 2 atypical cases. Although cited by Walker[16] as a case of atonic cerebral palsy, the patient reported by Koch[11] had spastic diplegia and showed flaccidity only terminally, three hours before death. The following case is presented because it represents a description of autopsy findings in a patient with atonic cerebral diplegia.

CASE REPORT

The gestation and delivery of this boy were not remarkable. The mother was 23 years of age at delivery, and the birth weight was 6 lb., 3 oz. There was no family history of neurologic disorder.

The parents first became concerned about him at 3 months, when he still was unable to hold up his head. At 7 months, a pediatrician suggested that he was mongoloid. Another pediatrician saw him at 18 months and believed that he was hypothyroid and prescribed thyroid, which was given for one and one-half years and discontinued at 3 years of age. Development continued to be slow, the patient being able to hold up his head only at 18 months. He had very little strength in his limbs. There was no attempt at toilet training, even at 3½ years. At 3½ years, he would grab at toys but not change objects from one hand to the other.

At 18 months, the patient began to have seizures. At first, these occurred 2 or 3 times daily. In them, he cried out, the arms flexed, the legs extended, the trunk became rigid, the eyes turned up, the eyelids fluttered, the face became red, and he salivated. The attacks lasted for a few seconds each, and, following them, he was sleepy for an hour or two. There were "goose bumps" on the body postictally, and he was sweaty at the end of an attack. The attacks tended to come on immediately after sleep, either in the morning or after naps in the daytime. Phenobarbital and later Dilantin and Mebaral were prescribed, with reduction in the frequency of seizures.

On examination at 3 years, 7 months, he did not follow light with his eyes and made no response to a bell. There was slight external strabismus. He was unable to sit up and made grunting sounds but no words. His limbs were flaccid, the lower limbs in a "frogleg" position and his arms moving in a purposeless athetoid manner. Normal myotatic reflexes were elicited bilaterally, and his plantar reflexes were normal. Sensory examination was inadequate because of lack of cooperation. His features were unusual: his head was long and narrow, and the frontooccipital circumference was 19¾ in. The base of his nose was broad.

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Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 16, 1959.

Fig. 1. Lateral view of right cerebral hemisphere, demonstrating frontoparietal agyria and enlargement of temporal lobe.

General examination showed no other abnormality. The diagnostic impression was congenital malformation of the brain with resultant mental and motor retardation and seizures of the "massive spasm" type.

An electroencephalogram made at 3 years, 8 months of age revealed generalized 1 to 3 per second waves and high voltage slow frontal spikes occurring asynchronously in the frontal regions.

Mebaral and Gemonil were given without effect. Mysoline and later Mysoline and Dilantin were given with reduction in the frequency of seizures, but seizures again increased in frequency about sixteen months later. These consisted of sudden throwing out of his arms and stiffening out of his legs, with blinking of his eyes. He had frequent respiratory infections, choked and coughed on food, and gradually lost weight.

At 5 years, 7 months, the physical examination was unchanged except for hypoactive myotatic reflexes and extensor plantar responses. Seizures continued, and occasionally massive flexion of the upper limbs and extension of the lower limbs were followed by generalized convulsions. The massive spasms occurred often in a series of 3 to 6 with each feeding but also came on spontaneously.

A repeat electroencephalogram at 6 years, 3 months showed generalized "variant" spike and slow wave abnormality, with very little activity of normal character. A seizure was observed during the recording and was characterized by the head drawing back, the arms flexing, and the legs pulling up on the abdomen. This persisted for six or seven seconds, and the patient then relaxed and appeared to sleep. During the seizure, there was "suppression" of the high voltage epileptiform activity, which was replaced by moderately low voltage fast activity in all leads.

Seizures continued, and the patient was unable to handle the accumulation of mucus in his throat. At 6 years, 8 months, he died following the aspiration of food.

Postmortem examination was performed six hours after death. There was evidence of partial to complete occlusion of the major bronchi by aspiration of mucohemorrhagic material and food. The lungs were hyperemic. There was moderate emaciation. Small atheromatous deposits were found in the aorta and the mitral and aortic valves.

The brain weighed 1,270 gm. after fixation. The cerebral hemispheres were bilaterally symmetric but long and narrow. Cerebral convolutions and sulci were present at the frontal pole and in the temporal and occipital lobes but were absent over a large part of the posterior frontal and all of the parietal cortex (Fig. 1). The temporal lobes seemed disproportionately large, especially posteriorly, the lateral fissure rising at an angle of approximately 45° from the horizontal. The leptomeninges were transparent except over the posterior end of the

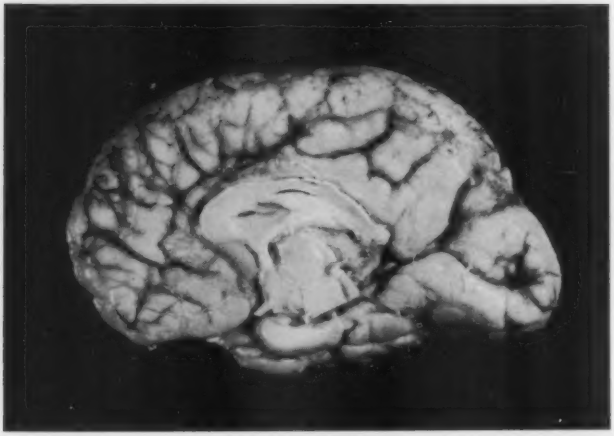

Fig. 2. Medial view of right cerebral hemisphere, demonstrating poorly developed sulci in frontal, parietal, and occipital regions.

left lateral fissure, where they were slightly cloudy over an area about 1 cm. in diameter. The vessels at the base of the brain were normal, but the branches of the middle cerebral artery were prominently visible as they splayed over the agyric posterior frontal and parietal areas. The cerebellum seemed generally small, the brain stem and cerebellum weighing only 95 gm., approximately 60% of the weight expected for the whole brain.[6] The cerebellar folia externally appeared of normal size.

Transection of the midbrain revealed the substantia nigra to be very pale and the basis pedunculi to be quite small (2.5 x 15 mm.). Horizontal sections of the brain stem and cerebellum revealed the fourth ventricle to be moderately enlarged. The spaces between the cerebellar sulci were increased, indicating some cerebellar atrophy. Inferior olives and pyramidal tracts were present, but there was no sulcus between them. The spinal cord appeared normal.

A midsagittal section through the cerebral hemispheres revealed the gyral pattern on the medial surfaces of the 2 hemispheres to be symmetric but very shallow (Fig. 2). The third ventricle and aqueduct were of normal size. There was no massa intermedia.

Coronal sections through the left cerebral hemisphere revealed the pattern of the cortex and white matter of the anterior temporal lobe to be approximately normal (Fig. 3). In the posterior temporal, posterior frontal, and parietal areas, however, the gray matter was very thick and poorly demarcated from the white matter at a level approximately 12 mm. beneath the pia mater. Posteriorly, in temporal, parietal, and occipital regions, the thick cortex was laminated into relatively thin external and thick internal layers separated by a narrow white band. The external lamina was about as thick as one would expect the normal cerebral cortex to be. The deep cerebral nuclei were normal except for the putamen, which seemed more narrow than usual. The body and frontal horn of the lateral ventricle were slightly enlarged and the temporal and occipital horns, moderately enlarged.

Blocks of representative portions of the central nervous system were embedded in paraffin, sectioned, and stained with hematoxylin and eosin, trichrome, Nissl, myelin, periodic acid–Schiff, Holzer, and silver (axon) stains. These not only confirmed the grossly obvious cerebral cortical malformation but also revealed malformations within the thalamus and medulla.

In the frontal lobe, the gray matter was very thick (6 to 15 mm.). This marked thickness of the frontal cortex gradually narrowed through the cingulate gyrus, the upper bank of which was about 4 mm. thick and the lower bank of which was only 2 mm. thick. The cingulate and inferior frontal sulci were present,

Fig. 3A. Coronal sections through central portion of left cerebral hemisphere, demonstrating agyria with marked thickening of frontoparietal and posterior temporal cortex.

Fig. 3B. Coronal sections through frontal *(above)* and occipital *(below)* lobes. Note white lamina dividing the thickened cortex into thin outer and thick inner zones. This lamination, also seen in (A), is not present in anterior frontal regions.

but the white matter was scarcely indented by these 2 sulci and no other frontal sulci were identifiable. In some Nissl preparations, there was no laminar pattern of the cortical neurons, which generally appeared decreased in number and arranged in irregular small clumps. Most of the neurons were pyramidal, with a vertical polarization, but some multipolar and other types of neurons were present. In other portions of the frontal lobe, the 2 superficial cortical laminae could be recognized, only the second layer having vertical columns of cells (Fig. 4). The third layer continued into the deeper portions of the gray matter, in which small fusiform neurons predominated, these continuing deep into the white matter as isolated cells.

The subcortical white matter was generally pale, but the corpus callosum was fairly well myelinated. Relatively few myelinated fibers penetrated deeply into the cortex, so that the demarcation between gray and white matter was not distinct. Within the white matter, there appeared to be an increased number of oligodendroglial cells occurring in groups between bundles of myelinated fibers, within which oligodendroglial cells were rare. This peculiar distribution of oligodendroglia was most marked in the immediately subcortical white matter (Fig. 5), in which the myelinated

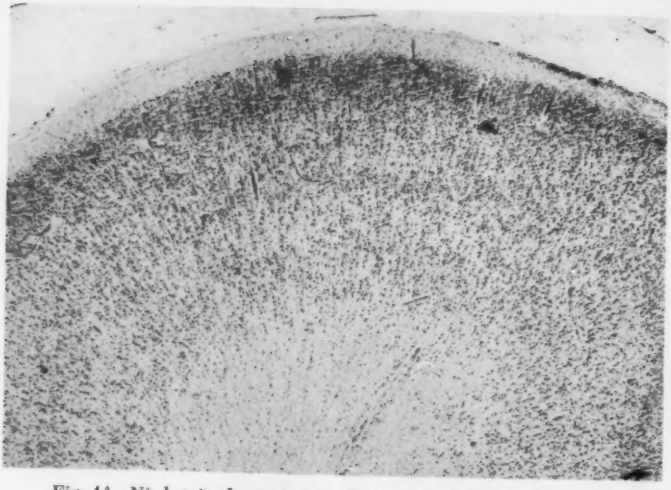

Fig. 4A. Nissl stained preparation of normal posterior frontal cortex

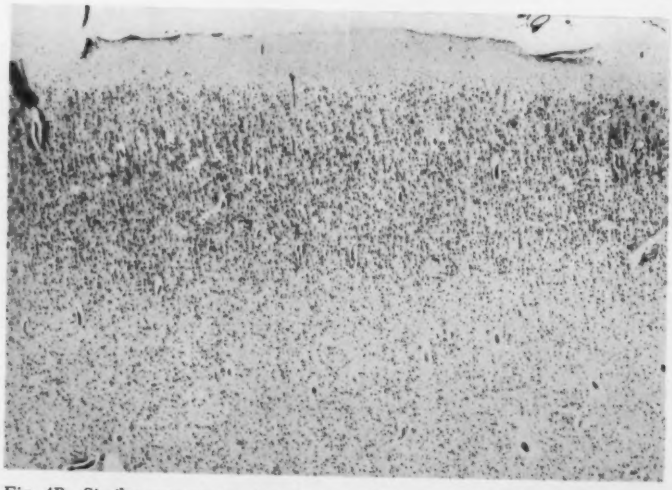

Fig. 4B. Similar preparation at same magnification of outer half of agyric posterior frontal cortex. Note decreased number of neurons and arrangement in vertical columns only in middle layer. The appearance of the deep layer in this photograph remained the same throughout the unphotographed deeper half of the agyric cortex.

fiber bundles were penetrating the deeper gray matter, but was evident even in the corpus callosum and periventricular white matter.

Sections through the insular and temporal cortex revealed the superior half of the insula to be thick, but this thickness gradually decreased in the inferior half of the insula, which was only 3 to 4 mm. thick. Similarly, the superior temporal gyrus was only 3 to 4 mm. thick. The middle temporal gyrus, however,

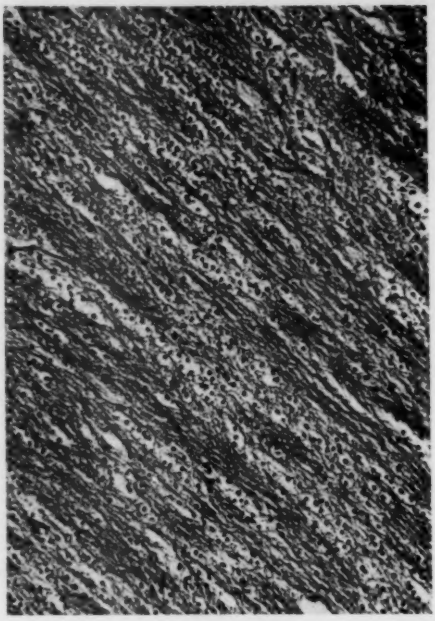

Fig. 5. Increased oligodendroglial cells in columns between medullated fibers in centrum semiovale. (Hematoxylin and eosin)

was fused with the inferior temporal and was at least 8 mm. thick. Within the fusiform and hippocampal gyri, the cortex again narrowed to about 3 to 4 mm. in thickness. In portions of the affected temporal cortex, the superficial 3 mm. appeared more normal with about the normal density of neurons, a thin molecular layer, a thin external layer of large pyramidal cells, and a thick layer of small pyramidal cells arranged in columns. The deeper 10 mm. were quite abnormal with no lamination, no columns of neurons, and a marked decrease in number of neurons. The subcortical white matter appeared pale. There was no evidence of gliosis or abnormal deposit of PAS-positive material.

Sections through the deep cerebral nuclei revealed the internal capsule both anteriorly and posteriorly to be only fairly myelinated and relatively thin (2 mm.). A heavily myelinated bundle entered the lateral-ventral thalamus from the internal capsule and partly contributed to the narrowness of the internal capsule. The thalamus was malformed, the lateral ventral nucleus being small and excessively myelinated from the internal capsule (Fig. 6). The internal medullary lamina was poorly developed, and there was a large aberrant tract lateral to the normal position of the mammillothalamic tract.

The hippocampus, uncus, and amygdaloid nucleus were relatively normal in appearance, as were the hypothalamus, globus pallidus, and striatum. The optic tracts, fornix, and anterior commissure were well myelinated. The temporal horn of the lateral ventricle was slightly

Fig. 6. Myelin sheath stained preparation of thalamus and striate body. Note thin internal capsule and aberrant tract in ventral lateral thalamus.

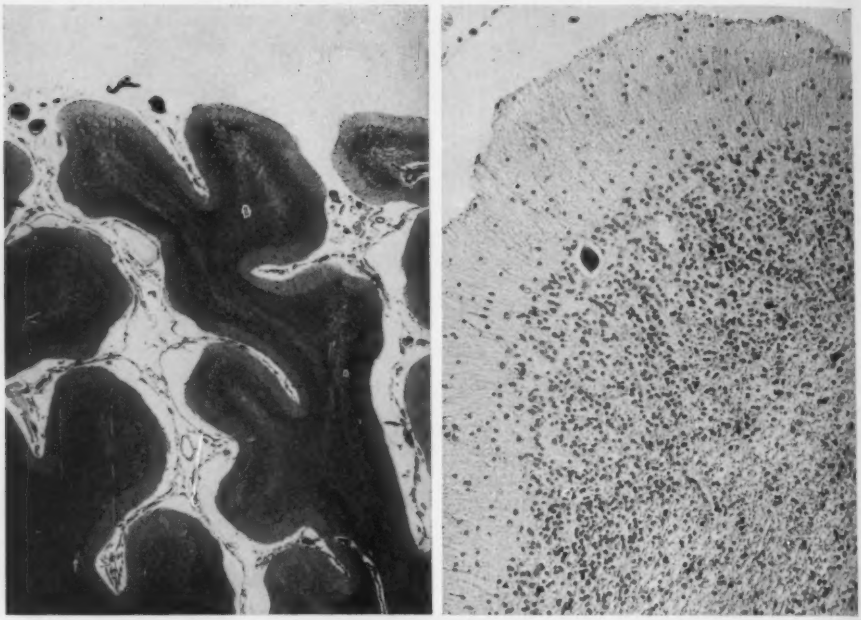

Fig. 7. *(Left)* Cerebellar cortex with almost complete loss of Purkinje cells and patchy loss of granule cells. Hematoxylin and eosin. *(Right)* High power view of cerebellar cortex, demonstrating single Purkinje cell, marked gliosis in Bergmann's layer, and marked reduction of granule cells. (Hematoxylin and eosin)

enlarged, and there were a few small subependymal granulations.

Sections of the cerebellar cortex revealed a marked, diffuse loss of Purkinje cells, with gliosis evidenced by increased number of nuclei within Bergmann's layer (Fig. 7). There was also a moderate diffuse gliosis of cerebellar cortex and white matter. The Purkinje cells were relatively better preserved in the vermis than laterally in the cerebellar hemisphere. Some of the Purkinje cells were displaced into the granular and molecular layers or even into the subcortical white matter. There was also a marked loss of cerebellar granule cells. This was more marked in some folia than in others and was patchy in distribution but was most marked at the crests of some of the folia. The white matter was well preserved except at the tips of the cerebellar folia, where the myelin sheaths and axons were decreased, especially as they entered the granular layer. No basket cells were seen in sections through the hemispheres, in which Purkinje cells were absent, and only very poorly formed basket cells were seen in the vermis, even where many Purkinje cells were present.

Sections of the midbrain revealed the basis pedunculi to be small. The periaqueductal gray matter was irregularly scalloped in outline. The aqueduct of Sylvius was moderately large, but there was no gliosis.

Sections of the medulla revealed the inferior olivary nucleus to be small, so that there was no bulge externally and no sulci dorsal or ventral to the olive (Fig. 8). There were bilaterally symmetric supernumerary nuclei just dorsal to the nucleus of the spinal tract of the trigeminal nucleus, ventral to the vestibular nucleus, medial to the restiform body and lateral cuneate nucleus, and lateral to the solitary tract and its nucleus. Around these supernumerary nuclei was an external capsule of myelinated

fibers resembling that about the main inferior olivary nucleus.[10] The cells within these aberrant nuclei were small and plump, with an eccentric nucleus similar to the cells of the inferior olive but slightly smaller. There was a rich neuropil among the cells. The dorsal accessory olivary nuclei were unusually large and round. The ventral arcuate nuclei were unusually large. The hypoglossal nuclei were poorly myelinated, but other systems within the medulla appeared normal, specifically the spinal trigeminal tract and its nucleus, the medial lemniscus, and the medial longitudinal fasciculus. The pyramids appeared unusually small but measured normal in area (7.03 sq. mm.) for this age.

Sections of the cervical and lumbar spinal cord appeared normal. There was no evidence of gliosis. A few PAS-positive granules were present in some of the anterior horn cells; other anterior horn cells contained small vacuoles and showed slight chromatolysis, but the number of neurons appeared normal.

Sections of skeletal muscle stained by hemotoxylin and eosin revealed most of the muscle fibers to be small, although there was considerable variation in fiber size, from 8 to 45 μ in diameter. There was no pattern or grouping of the small fibers or relative increase in number of muscle nuclei. Indeed, many fibers in cross section had only 1 nucleus, which was peripherally placed, and many of the small fibers had no nucleus in the plane of section. The muscle otherwise appeared normal, as did the peripheral nerves and muscle spindles.

Fig. 8. Myelin sheath stained preparation of middle medulla, demonstrating hypoplasia of inferior olivary nuclei and pyramidal tracts with symmetric supernumerary nuclei in dorsolateral quadrants. These supernumerary nuclei probably represent unmigrated aberrant inferior olivary nuclei.[10]

DISCUSSION

Differential diagnosis. Because of the occurrence of flaccid weakness dating from birth, the diagnosis of amyotonia congenita is often considered for patients with atonic cerebral palsy. The differentiation of these conditions is seldom difficult because of the absence of myotatic reflexes in amyotonia congenita and the hyperactive or normally active reflexes in atonic cerebral diplegia. Furthermore, in amyotonia congenita, the mentality is normal, whereas mental retardation is characteristically present in atonic cerebral palsy.

Clinicopathologic correlation. The location of the lesion or lesions responsible for the lack of tone in atonic cerebral diplegia is not known. Yannet[19] has studied the morbid anatomy of 4 patients with atonic cerebral diplegia, and, in these, the only common factor was smallness of the brain. Of the 4 patients, 3 showed diminution in the number of cerebral cortical neurons, 1 showed patchy focal loss of Purkinje and granule cells in the cerebellum, and 2 sisters had loss of cells in the globus pallidus. Clark[3] believed that the lack of tone was due to a cerebellar lesion but had no autopsy evidence for this.

If the location of the lesion responsible for flaccid hemiplegia in man were known, it might provide a clue to the expected location of the lesion in atonic cerebral diplegia. Davison and Bieber[4] found thalamic and "other deep-seated" lesions in some of their cases. Mayendorf[13] emphasized the demyelination deep to the island of Reil as interfering with a postulated function of the central cerebral convolutions in the maintenance of tone. Verhaart[15] believed that extensive involvement of sensory pathways was a necessary concomitant of "pyramidal" lesions in the production of flaccid hemiplegia. He found lesions of the lateral thalamic nucleus in most of his cases of flaccid hemiplegia. Aring,[1] in his study of 3 cases, concluded that the flaccidity in flaccid

hemiplegia was due to destruction of the striatum and its radiations.

Thus, flaccidity of cerebral origin has been attributed to lesions of the cerebral cortex, subcortical white matter, striatum, lateral nucleus of the thalamus, or cerebellum. Other possible sites of lesions responsible for decreased tone are brain stem, spinal cord, peripheral nerve, and skeletal muscle. In our case, since the skeletal muscle and spinal cord revealed no abnormality, a suprasegmental lesion presumably was responsible for the lack of tone. The cerebellar lesions in this case are the ones frequently seen in seizure patients.[10] In view of the multiplicity of lesions present, it appears impossible to attribute the atonicity to a lesion of any one site, for example, to interruption of facilitation of tone at the cerebral cortical, thalamic, brain stem, or cerebellar level.

In other reported cases of lissencephaly, the clinical picture was of spastic rather than atonic cerebral palsy. The factors responsible for lack of tone in this case rather than the increased tone found in other cases of lissencephaly[11,12,16,17] remain unknown.

This case report is of interest, too, in relation to the morbid anatomy of the "massive spasm" seizure pattern. The findings here support the inference, based upon clinical data, that diffuse and severe brain damage is responsible for massive spasms.[7] Since gross abnormalities are present in the formation of both cerebral cortex and brain stem, it is not possible to relate the seizure manifestations to disturbance at either site. It is of interest that the seizures present in one (Case 3) of the cases of schizencephaly reported by Yakovlev and Wadsworth[17] were of "massive spasm" type.

SUMMARY

The clinical features of atonic cerebral diplegia are hypotonia, weakness, marked delay in motor development, mental retardation, and frequently associated convulsive disorder. Although this form of cerebral palsy has been estimated to affect 5 to 10% of institutionalized patients with cerebral palsy, this description of the autopsy findings appears to be the first in a case of typical atonic cerebral diplegia.

The patient was slow in development and had seizures of "massive spasm" type. On examination, he showed lack of muscle tone with normal myotatic reflexes and unusual facial features. He died at 6 years, 8 months of aspiration of food.

Autopsy revealed lissencephaly with anomalous formation of cerebral cortex, cerebellum, thalamus, and medulla. In addition, loss of Purkinje cells and gliosis were interpreted as secondary to anoxia with seizures.

The correlation of clinical and pathologic findings is discussed.

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Effects of changes in composition of plasma on pial blood flow

II. High molecular weight substances, blood constituents, and tonicity

Arthur G. Waltz, M.D., and John S. Meyer, M.D.

In a previous communication, we have described the changes occurring in the pial circulation following the administration of lipid and lipid fractions to several species of experimental animals.[1] It is well established that the addition to the blood of certain naturally occurring substances of high molecular weight, such as gum acacia, bacterial polysaccharides, gelatin, and other proteins, alter the suspension stability and viscosity of the blood.[2–8] Resulting erythrocyte aggregation and rouleau formation have been observed both in vitro and in vivo. In vivo, these effects have been noted in the small vessels of the mesentery of the rat and the cheek pouch of the hamster. Recently, it has been shown that synthetic preparations of high molecular weight can produce aggregation of erythrocytes in vivo and in vitro.[4–6] Certain of these preparations, such as dextran and polyvinylpyrrolidone (PVP), are used as plasma expanders in clinical practice. It is also well known that, in polycythemia vera, the viscosity of the blood and the erythrocyte sedimentation rate increase.

The present study was designed to examine the effects of high molecular weight substances on the cerebral circulation. These observations may aid in an analysis of the series of events which leads to circulatory slowing, stasis, and infarction after the occlusion of cerebral vessels and may provide information of theoretic importance in the treatment of human subjects suffering from cerebrovascular disease.

MATERIALS AND METHODS

In these studies, 21 cats and 1 monkey (Macaca rhesus) were used. The methods of preparation of each animal and the technical details have been described previously.[1] In brief, the animals were fasted, and light anesthesia was induced with pentobarbital. The pial surface of the right cerebral hemisphere was exposed, and the right middle cerebral artery was occluded to produce a zone of relative ischemia. For comparison, the pial circulation of the left cerebral hemisphere was also exposed but left intact. The abdominal aorta was catheterized via the femoral artery to permit continuous recording of the blood pressure and recognition of artifactual change due to hypotension. In addition, the inferior vena cava was catheterized via the femoral vein, so that the experimental substances could be introduced by slow intravenous infusion. In general, the amount administered was equivalent to one-quarter of the estimated blood volume of the animal.

Observations and photographs of the ischemic and nonischemic zones were made prior to and at intervals following the administration of the substances under study. The use of 2 35-mm. single lens reflex cameras, each fitted with extension tubes and single objective lens, allowed the direct observation of the areas being photographed. Magnifications at the film were x30 in the ischemic zone and x10 in the nonischemic zone, with resultant magnifi-

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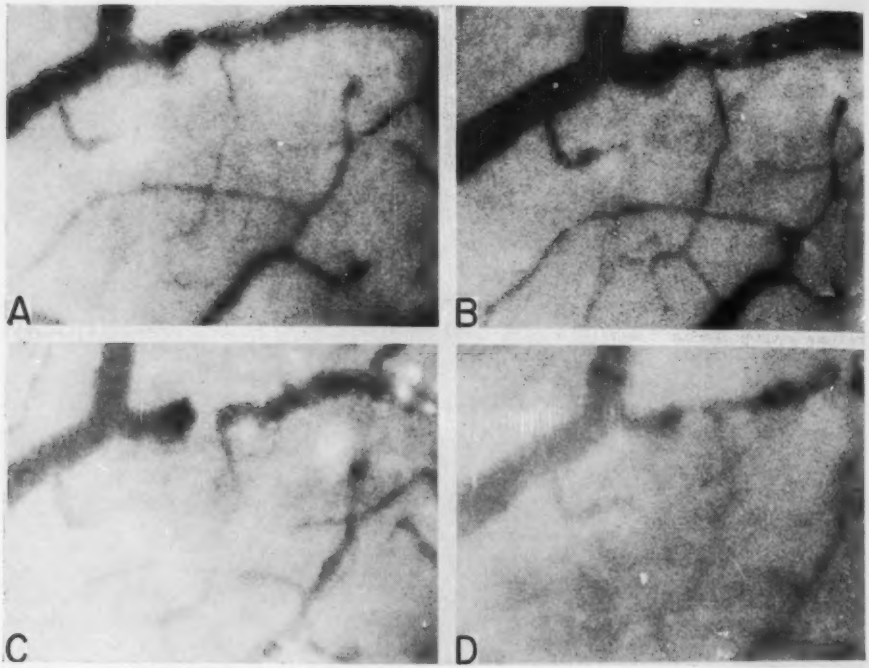

Fig. 1. (× 100) Changes occurring in pial circulation after slow intravenous administration of physiologic saline solution, followed by an amylopectin with average molecular weight of 1,000,000 (Ramalin). [A] Pial circulation one hour after occlusion of middle cerebral artery. [B] Two hours after administration of physiologic saline solution equal to one-fourth of estimated blood volume. No change is noted. [C] One hour after amylopectin. Aggregation and clear plasma-filled space are seen in a large transverse vein. [D] Two hours after amylopectin

cations of x240 and x80, respectively, on an 8 x 10 in. print.

Samples of peripheral blood were drawn from the catheter inserted into the inferior vena cava and examined before and after the administration of the experimental substances. Each sample consisted of 1.8 cc. of blood, which was mixed with 0.2 cc. of 3.2% sodium citrate. A blood smear was prepared and examined with a dark-field illuminator and microscope. A quantitative estimation of rouleau formation and chylomicronemia was made, and the smear was photographed. The remainder of the sample of blood was used for determinations of the corrected erythrocyte sedimentation rate (Wintrobe), hematocrit, plasma turbidity, plasma recalcification time (P.R.C.T.), and Russell viper venom time (R.V.T.).

RESULTS

Control studies. The changes occurring in the pial circulation and peripheral blood during prolonged observation (six to eight hours) of these preparations have been reported by us previously.[1] Observations also have been made of the effects of the infusion of isotonic saline solution (0.85%). The latter group of experiments provided additional control observations. In the group given nothing, narrowing of larger vessels occurred after four to six hours, with some disappearance of smaller vessels from the capillary bed.[1] No changes were seen after the infusion of physiologic

TABLE 1
PERIPHERAL BLOOD STUDIES: CONTROL AND HIGH MOLECULAR WEIGHT POLYSACCHARIDES AND PLASMA EXPANDERS

Animal and sample	*Chylomicrons*	*Rouleaux*	*Hct*	*ESR corrected*	*Turbidity*	*P.R.C.T.*	*R.V.T.*
FAC 25 (Cat) 1.	3–5/H.P.F.	30%	27%	32 mm./hr.	0	4.5 min.	19 sec.
2. PSS—2 hr.	50–70	100	28	31	0	3	19
3. Ramalin—2 hr.	8–10	60	28	24	0	4	16
FAC 21 1.	2– 4	60	35	44	0	3.5	17
2. Dextran—3 hr. (Avg. MW 75,000)	8–15	100*	24	32	0	6.5	25
FAC 34 1.	0– 2	20	28	0	0	3	17
2. PVP—1 hr. (Avg. MW 360,000)	0– 3	100*	23	30	0	30	27
FAC 36 1.	0– 4	30	35	0	0	3	18
2. PVP—1 hr. (Avg. MW 160,000)	0– 1	60*	20	27	0	30	120
FAC 22 1.	0– 2	15	27	35	0	3	18
2. PVP—2 hr. (Avg. MW 50,000)	5– 7	90*	22	31	0	3	23
FAC 37 1.	0– 1	60	32	0	0	2	12
2. PVP—1 hr. (Avg. MW 14,000)	0– 1	100	29	9	0	2	15

1. Steady state values
* Distortion and "stickiness" of erythrocytes present
PSS = 0.85% saline solution

saline solution (Fig. 1*A* and *B*); in particular, no erythrocyte aggregation, segmentation, stasis, or slowing of flow was noted as long as the blood pressure was maintained. In addition, no changes were observed in the peripheral blood (Table 1) nor was there any consistent change in hematocrit or erythrocyte sedimentation rate.

Effects of high molecular weight polysaccharides and plasma expanders

Changes in pial circulation. A 6% solution of commercial dextran in 0.85% saline (Cutter), having an average molecular weight of 75,000, was allowed to drip slowly into the vena cava until the total amount administered was approximately one-fourth the estimated blood volume of the animal. Within thirty minutes, there was aggregation of erythrocytes in the pial vessels followed by slowing of the flow of blood. In early stages, aggregation imparted a granular or particulate appearance to the columns of blood visible in arterioles and venules (Fig. 2*B*). Similar changes occurred after the administration of an equivalent amount of a 3.5% solution of commercial PVP (Schenley Laboratories) with an average molecular weight of 50,000 (Fig. 3) and after the administration of a 6% solution of a commercially prepared amylopectin (Ramalin, Stein, Hall Co.) having an average molecular weight of 1,000,000 (Fig. 1*C* and *D*). After the injection of these high molecular weight substances, aggregation of erythrocytes and slowing of the flow of blood occurred in both ischemic and nonischemic areas. At times, the aggregation of erythrocytes progressed to the point of segmentation and stasis of the columns of blood in small vessels (Fig. 3*B*). This degree of aggregation was prominent only in areas made ischemic by occlusion of the right middle cerebral artery.

The same changes were produced, but to a greater degree, by 5% solutions of PVP of higher average molecular weight (160,000 and 360,000). However, a 5% solution of PVP with an average molecular weight of 14,000 did not result in aggregation.

Changes in peripheral blood. The effects that the administration of these materials had on the peripheral blood are summarized in Table 1. None of the high molecular weight polysaccharides or plasma expanders produced chylomicronemia. The difficulties of interpretation of quantitative differences in rouleau formation in smears of peripheral blood have been discussed previously.[1] However, an increase in the percentage of erythrocytes found in rouleaux after the infusion of high molecular weight dextran or PVP was present consistent-

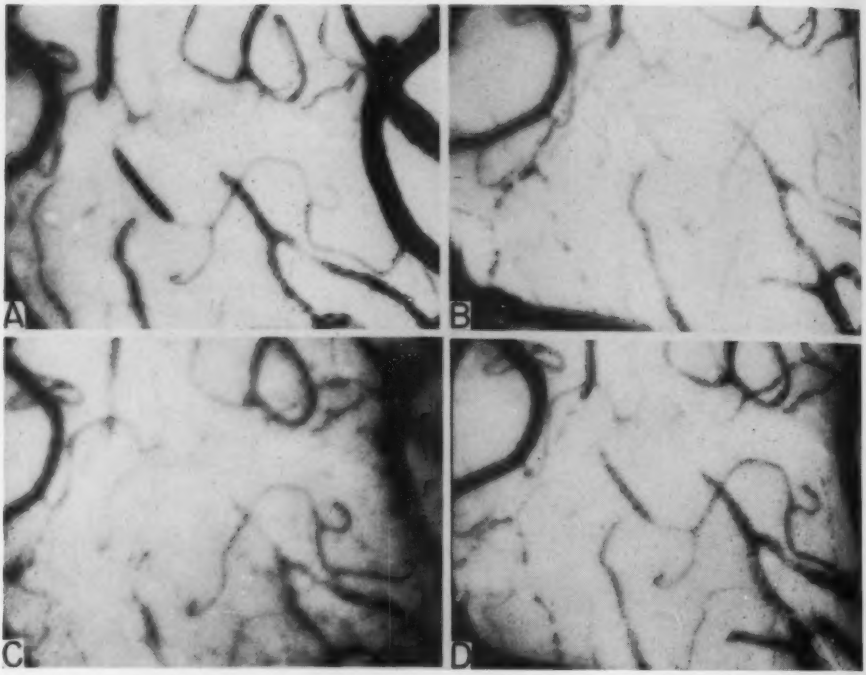

Fig. 2. (× 107) Changes after intravenous administration of dextran (75,000). [A] Pial circulation one hour after occlusion of middle cerebral artery. [B] Thirty minutes after dextran. Aggregation and segmentation are present. [C] Two hours after dextran. [D] Four and one-half hours after dextran

ly. In addition, gross clumping of erythrocytes was noted (Fig. 4*C*), and there was a remarkable distortion of erythrocytes. The red cells became firmly adherent to one another and resisted separation. When streaming of the blood beneath the cover glass caused the cells to separate, they first became elongated in a biconvex manner (Fig. 4*D*). With further separation, a thin strand of material became visible, stretched between adjacent erythrocytes. These strands occasionally reached great lengths (Fig. 4*B*) before eventually rupturing, at which time the usual biconcave appearance of the erythrocytes was restored. It was not possible to ascertain by observation whether these strands were parts of the capsules of the erythrocytes or whether they were composed of the high molecular weight substance adsorbed on the surface of the erythrocytes.

The corrected erythrocyte sedimentation rate frequently increased after administration of these high molecular weight substances, in association with the increase in rouleau formation and the distortion and "stickiness" of the erythrocytes. The correlation was not absolute, however, and, at times, the sedimentation rate decreased despite the presence of increased rouleau formation. In general, the hematocrit decreased following the injection of these materials. Turbidity of the plasma was not changed. The 2 studies of the coagulability of the blood (P.R.C.T. and R.V.T.) did not give evidence of hypercoagulability. Rather, high molecular weight dextran and PVP acted as anticoagulants, increasing clotting time.

PVP of relatively low molecular weight (14,000) did not produce a striking change in the aggregation of erythrocytes as noted in

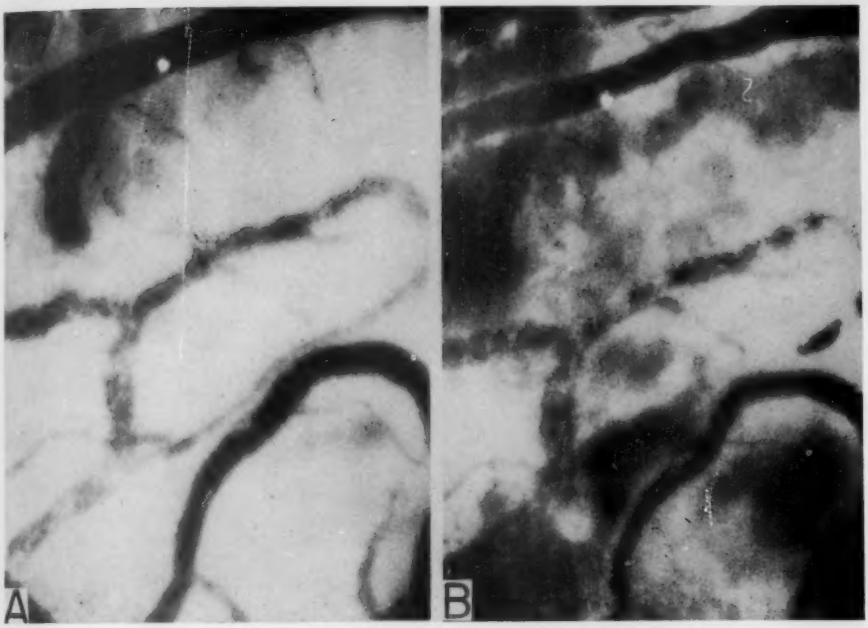

Fig. 3. (× 154) Changes after intravenous administration of PVP (50,000). [A] Pial circulation one hour after occlusion of middle cerebral artery. [B] Thirty minutes after PVP. Increased aggregation and segmentation of erythrocytes are present.

the smears of the peripheral blood nor did it increase the clotting times. Amylopectin of molecular weight of 1,000,000 likewise did not produce such remarkable changes in the peripheral blood but did produce aggregation within the pial vessels.

Effects of increases in blood constituents

Changes in pial circulation. After the infusion of packed homologous erythrocytes suspended in physiologic saline solution (hematocrit of administered material, 50%) in an amount equivalent to one-fourth the estimated blood volume of the animal, there was an immediate increase in the diameter of pial arteries and veins, with an apparent increase in the density of the blood and a marked slowing of flow (Fig. 5*B*). Within thirty to forty-five minutes, there was gradual restoration of the rate of flow in nonischemic areas but, in areas made ischemic by occlusion of the middle cerebral artery, aggregation of erythrocytes developed and eventually progressed to segmentation and stasis (Fig. 5 *C* and *D*). These results were not obtained in 2 animals given a mixture that, on examination, was found to have become hemolyzed.

The intravenous injection of 3 gm. of bovine fibrinogen (Armour) having an average molecular weight of 500,000 also produced intravascular aggregation of erythrocytes but no segmentation or stasis. Human serum albumin (average molecular weight, 67,000), given in an amount equivalent to one-fourth the estimated blood volume of the animals, did not produce aggregation of erythrocytes.

The administration of a minute quantity of purified thrombin (Parke, Davis and Co.) resulted in immediate and total intravascular coagulation of blood in the pial vessels. Material sufficient to do this remained in a polyethylene catheter that had been carefully washed after its use for the administration of thrombin in a preceding experiment.

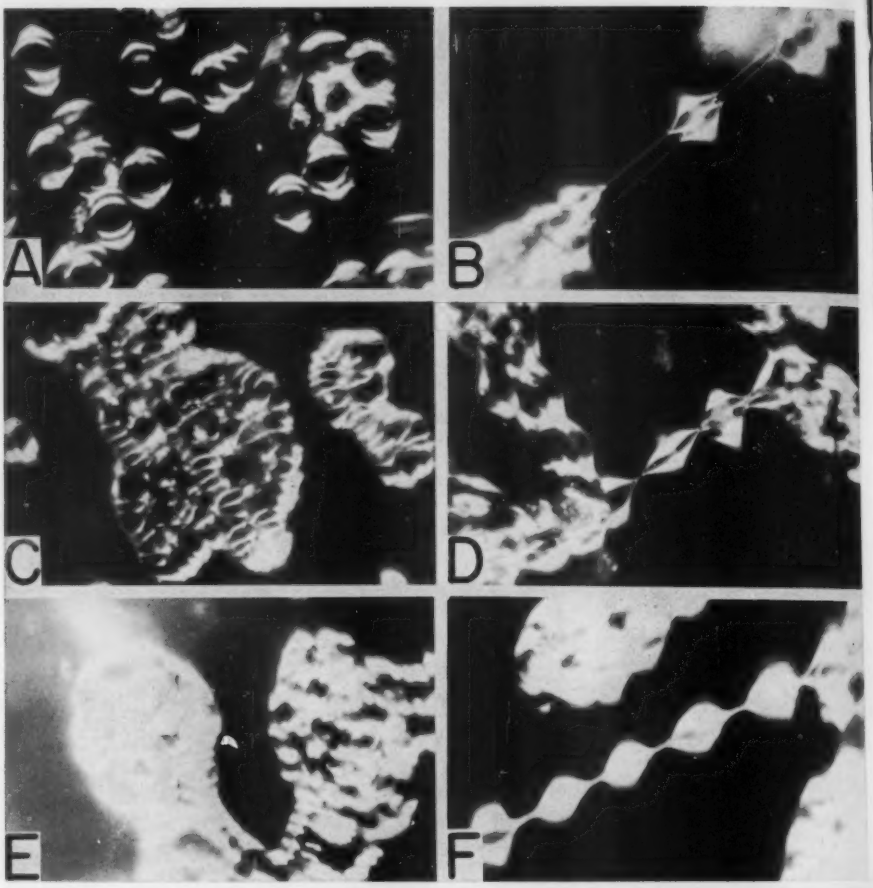

Fig. 4. (× 930) Dark-field photomicrographs of smears of peripheral blood samples. [A] Sample drawn before the introduction of experimental variable. [B] Sample drawn two hours after intravenous infusion of dextran with an average molecular weight of 75,000. [C] Sample drawn one hour after intravenous infusion of PVP with an average molecular weight of 50,000. [D] Sample drawn three hours after intravenous infusion of PVP with an average molecular weight of 50,000. [E] Sample drawn two hours after experimental erythrocythemia (hemoconcentration) had been produced by infusion of packed homologous erythrocytes. [F] Sample drawn thirty minutes after infusion of packed erythrocytes (see text for details).

Changes in peripheral blood. The effects of the intravenous administrations of the substances are summarized in Table 2. The infusion of a suspension of packed homologous erythrocytes (hematocrit, 50) in physiologic saline solution produced much the same effect on peripheral blood as did the administration of high molecular weight dextran and PVP. There was an increase in rouleau formation, and clumping, distortion, and "stickiness" of the erythrocytes were prominent (Fig. 4*E* and *F*). The corrected erythrocyte sedimentation rate and the hematocrit were increased, and clotting studies showed, if anything, a transient

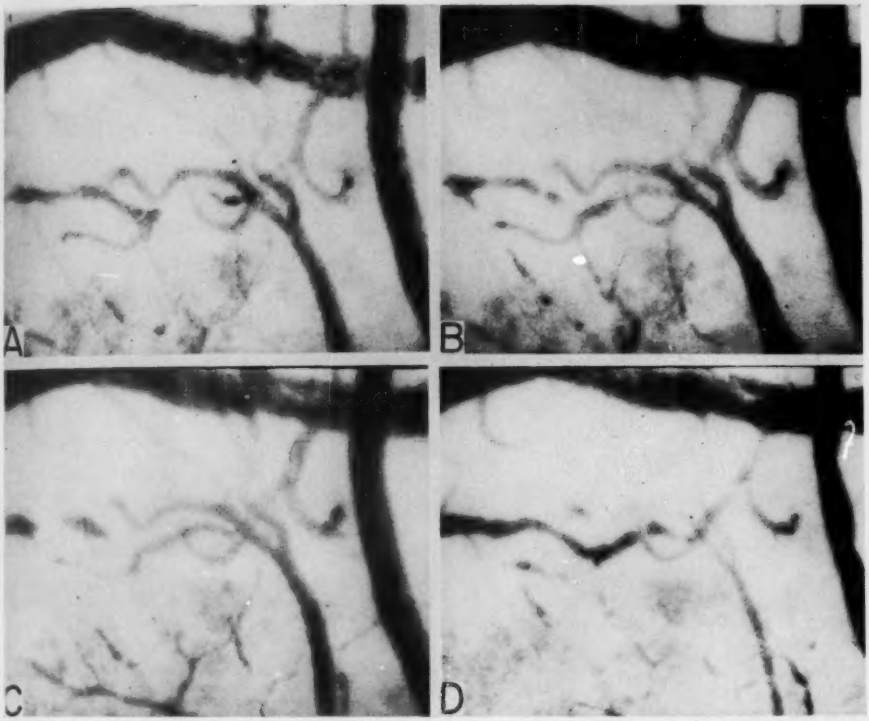

Fig. 5. (× 100) Effects of experimental erythrocythemia (hemoconcentration). [A] Pial circulation one hour after occlusion of middle cerebral artery. [B] Fifteen minutes after slow intravenous administration of packed homologous erythrocytes. Note larger caliber of pial vessels. [C] Forty-five minutes after erythrocytes. [D] One and one-half hours after erythrocytes, aggregation and early segmentation are present.

TABLE 2

PERIPHERAL BLOOD STUDIES: BLOOD CONSTITUENTS, HYPERTONICITY, AND HYPOTENICITY

Animal and sample	*Chylomicrons*	*Rouleaux*	*Hct*	*ESR corrected*	*Turbidity*	*P.R.C.T.*	*R.V.T.*
FAC 23 1.	15–18/H.P.F.	60%	23%	26 mm./hr.	0	16.5 min.	25 sec.
2. RBC—1 hr.	12–15	100%*	37	46	0	8.5	28
FAC 48 1.	0– 3	85	26	0	0	1	11
2. Hemolyzed RBC—1 hr.	100–150	60	23	0	Hem.†	2.5	12
FAC 26 1.	3– 5	40	32	0	0	2	15
2. Fibrinogen—1 hr.	3– 5	60	29	37	0	5.5	14
FAC 24 1.	0– 3	40	36	0	0	4	22
2. Albumin—1 hr.	0– 3	0	18	0	0	6.5	43
FAC 30 1.	0– 3	70	23	10	0	2	12
2. 15% NaCl—1 hr.	0– 3	50	21	6	0	2.5	12
FAC 27 1.	8–10	100	29	0	0	2	14
2. 30% urea—2 hr.	3– 5	60	27	0	0	2	14
FAC 32 1.	0– 3	90	27	2	0	2.5	21
2. Distilled water—1 hr.	0– 3	85	19	0	0	2	16

* Distortion and "stickiness" of erythrocytes present † Hemolyzed

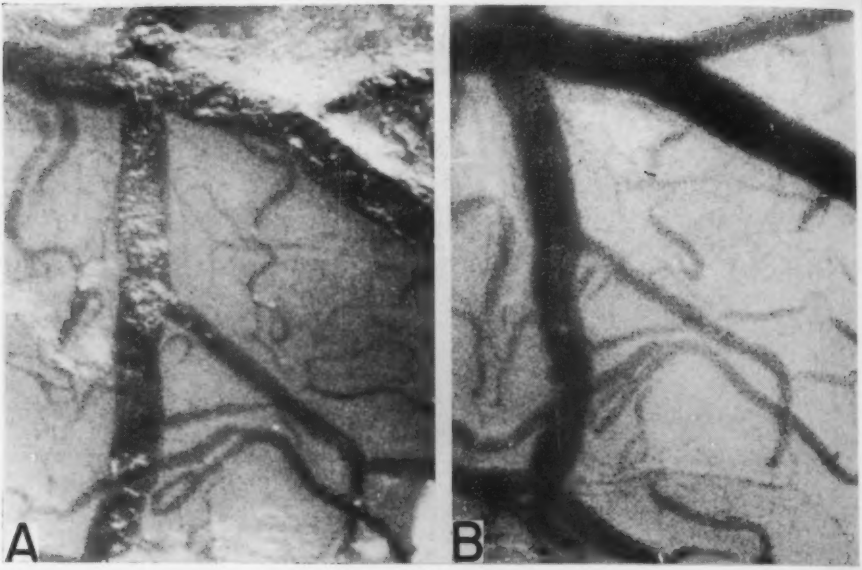

Fig. 6. (× 65) Effects of hypertonicity. [A] Pial circulation exposed. Middle cerebral artery has not been occluded. [B] Thirty minutes after slow intravenous administration of a 30% urea and 10% glucose solution. Note absence of aggregation.

tendency toward hypercoagulability. These changes were not noted in animals given hemolyzed blood.

The intravenous administration of bovine fibrinogen resulted in increased rouleau formation and erythrocyte sedimentation rate but did not significantly affect other blood studies. Human serum albumin produced hemodilution and slightly decreased blood coagulability.

Effects of changes in tonicity of the blood

Changes in pial circulation. The effects of hypertonicity of the plasma were examined following the slow intravenous infusion of a solution of 15% sodium chloride and a solution of 30% lyophilized urea in 10% glucose. The solutions were administered in a total volume equivalent to one-fourth the estimated blood volume. During the infusion, there was some increase in the diameter of the small blood vessels in the intact hemisphere. A marked decrease in the size of the brain occurred within fifteen to thirty minutes, but there was no observable aggregation of erythrocytes or change in the flow of blood (Fig. 6). During the stage of maximal shrinkage of the brain, bridging veins between the pia-arachnoid and the dura were severely stretched in areas in which the skull was left intact. However, rupture with subdural or other hemorrhage did not occur.

Hypotonicity was induced by the administration of a similar volume of distilled water. This produced marked cerebral edema with distention of both arterioles and veins but no aggregation of erythrocytes or change in the flow of blood.

Changes in peripheral blood. The effects on the peripheral blood are summarized in Table 2. Neither hypertonicity nor hypotonicity resulted in significant or consistent changes in the venous blood as measured by the studies performed. There was no consistent change in the hematocrit at the time the blood samples were drawn, which was one to two hours after the administration of the experimental solution.

DISCUSSION

In a previous communication, the series of events that occur in the small cerebral vessels following vascular occlusion has been described.[9] Unless there is preservation of flow by the collateral circulation, slowing of the flow of blood occurs in the ischemic territory, along with local tissue hypoxia. The normal axial streaming of the blood cells is disrupted, with resultant turbulent flow and margination of leukocytes. Anoxic damage to the vascular endothelium leads to localized loss of plasma with hemoconcentration in the ischemic vessels, and aggregation of erythrocytes begins on the venous side of the capillary net. This produces further slowing of flow, the appearance of segmentation, and, ultimately, stasis with infarction.

The present series of experiments was undertaken to analyze in detail certain localized changes in the composition of the plasma, which can result in intravascular aggregation of erythrocytes and contribute significantly to the process of infarction.

It is apparent from these experiments that the addition of high molecular weight substances not normally present in the blood (dextran, PVP, or amylopectin) or an increase in the content of at least 1 high molecular weight substance that occurs naturally in the blood (fibrinogen) produces intravascular aggregation of erythrocytes. Aggregation of erythrocytes occurs diffusely throughout the pial circulation, but the phenomenon is most marked in areas of relative ischemia.

The most effective method of producing intravascular aggregation is by inducing experimental erythrocythemia or hemoconcentration with the transfusion of fresh, packed, homologous erythrocytes. This results in diffuse slowing of blood flow with aggregation, segmentation, and stasis in areas of relative ischemia. The infusion of an equal volume of lysed erythrocytes does not produce any change. Thus, the responsible factor in erythrocythemia may be the increase in the number of erythrocytes themselves, although it is probable that some fibrinogen and other blood elements are introduced with the infusion. It is well known that polycythemia vera causes a marked increase in the viscosity of the blood, which would appear, from these studies, to be due in part to an increased adhesiveness of erythrocytes. The tendency of erythrocytes to aggregate in rouleaux after hemoconcentration is partially explained by the increased frequency of cellular collision,[2] but this does not explain increased "stickiness" as demonstrated by their distortion on separation.

With the administration of high molecular weight substances such as dextran and PVP, it is clear that a significant change in the physical properties of the erythrocytes occurs. A thin film of material can be seen between the cells as they separate from one another. This film may consist of the adsorbed high molecular weight material or may be the distorted and stretched membrane of the erythrocyte itself. We believe that the former is more likely, but our observations do not permit further conclusions regarding the exact nature of these adherent strands. It is apparent, however, that the normally repellent negative electrical charge of erythrocytes is affected, and the most likely explanation for this change is that it is due to the adsorption of high molecular weight substances on the surface of the erythrocytes.

Substances of high molecular weight that produce this phenomenon include polysaccharides, proteins, and lipids.[1] In general, the higher the molecular weight of the substance, the more effective it is in producing aggregation. Nevertheless, some substances appear to be more effective than others of comparable molecular weight. For example, albumin (67,000) produces little if any effect, whereas PVP (50,000) produces definite erythrocyte aggregation. PVP of lower molecular weight (14,000) is ineffective. This finding is in agreement with that of Thorsen and Hint,[4] who found that different substances have different critical molecular weights for inducing the phenomenon of erythrocyte aggregation.

Once high molecular weight substances are introduced into the circulation, aggregation of erythrocytes is rapid. It is regularly established within thirty minutes, and, in some experiments, intravascular aggregation of erythrocytes can be observed while the infusion is in progress. The appearance of intravascular aggregation of erythrocytes is the same whatever the substance used and begins with a particu-

late appearance of the flow in small arterioles and venules, followed by the development of larger aggregates of erythrocytes, segmentation, slowing of flow, and, in areas of ischemia, stasis. The aggregates of erythrocytes are orange-red at first, but, when the flow becomes sufficiently slow or stagnant, cyanosis follows.

The changes in the peripheral blood following the injection of high molecular weight substances parallel the changes in the pial vessels and consist of an increase in the corrected erythrocyte sedimentation rate, an increase in rouleau formation in smears of the blood, and a tendency to distortion of erythrocytes on separation. The studies of the coagulability of the blood appear to exclude changes in the over-all clotting mechanism as the cause of aggregation of erythrocytes. Dextran and PVP have anticoagulant properties, and no significant changes were noted in the clotting of the blood after the infusion of other high molecular weight substances, with the exception of thrombin. The introduction of thrombin intravenously produces an entirely different result, diffuse intravascular clotting in all the pial vessels, which appears as a solid column of coagulated blood. Erythrocyte aggregation, segmentation, and stasis do not occur. Thrombin was administered to 2 animals only, since they promptly died after its introduction.

The effects of changing the tonicity of the blood were examined because ischemic anoxia results in brain swelling, and it was considered possible that this might affect blood flow in the small pial vessels. In the type of preparation used in this series of experiments, the brain was permitted to swell without restriction. The intravenous infusion of distilled water caused as much as 7 mm. of lateral enlargement of the brain without visible change in pial blood flow. If a cranial window is used, however, severe brain swelling is known to produce compression of small vessels against the window with obstruction of the flow of blood.[9] Changes in the flow of erythrocytes were not noted following infusions of hypertonic saline or urea.

This study of the effects of changes in composition of the plasma on pial blood flow concurrently in normal and ischemic areas permits certain conclusions to be made concerning the alterations in local hemodynamics, which may culminate in cerebral infarction. After the occlusion of a cerebral vessel, slowing of the flow of blood predisposes the erythrocytes in the area to aggregation, partly because turbulent flow increases the frequency of cellular collision.[2] Aggregation of erythrocytes does not occur if the collateral circulation is adequate, however, unless the concentration and nature of the plasma colloids are altered or the number of erythrocytes in the circulating blood is increased.

If the collateral circulation fails in an area of ischemia, anoxia begins on the venous side of the capillary bed and endothelial damage results.[9] There is a loss of plasma fluid causing localized hemoconcentration, erythrocythemia, and an increase in the plasma colloids. Landis has shown that this phenomenon occurs normally in the vascular bed elsewhere in the body.[10] The intact capillary endothelium is freely permeable to water and to solutions of most salts but is relatively impermeable to the colloidal plasma proteins. It has been shown that, after three minutes of anoxemia, fluid filters through the capillary wall 4 times more rapidly than before anoxic damage.[10] As a result of loss of plasma water in the area of ischemia, localized hyperproteinemia and erythrocythemia occur. This results in intravascular aggregation of erythrocytes and a localized increase in the viscosity of the blood.

Endogenous systemic factors that may increase the likelihood of cerebral infarction include polycythemia, erythrocythemia, hemoconcentration, and dehydration. Exogenous systemic factors that predispose ischemic brain to infarction include the introduction of high molecular weight substances into the circulating blood. Important in this respect are postprandial lipemia and the infusions of high molecular weight plasma expanders such as dextran and PVP. Conversely, factors that tend to influence the course of cerebral ischemia favorably include the prevention of dehydration, hemoconcentration, and erythrocythemia; correction of polycythemia if it exists; and the avoidance of the introduction of high molecular weight substances into the circulating blood.

CONCLUSIONS

1. The intravenous infusion of high molecular weight polysaccharides and plasma ex-

panders (dextran, PVP, and amylopectin) results in aggregation of erythrocytes within small pial blood vessels. In general, substances having a molecular weight in the range of 50,000 to 100,000 or more produce these changes. This effect appears to be diffuse throughout the brain but is always greater in areas of relative ischemia, in which segmentation and stasis of the blood may lead to infarction.

2. High molecular weight substances (dextran, PVP, and amylopectin) introduced into the blood stream tend to cause increased rouleau formation and adhesiveness of erythrocytes in smears of the peripheral blood, as well as in vivo. In addition, the erythrocyte sedimentation rate tends to increase after the injection of these substances.

3. An increase in certain constituents of the blood (erythrocythemia and hyperfibrinogenemia) produces effects in blood smears and in the pial circulation which are comparable to those following the introduction of high molecular weight dextran, PVP, and amylopectin.

4. The changes in the pial circulation produced by the introduction of high molecular weight substances and by erythrocythemia are not related to any demonstrable increase in the coagulability of the blood.

5. Hypertonic and hypotonic solutions (saline and urea) do not affect the flow of erythrocytes within the pial vessels, despite the occurrence of gross swelling or shrinkage of the brain, unless brain swelling results in mechanical compression of vessels.

6. After the occlusion of a cerebral vessel, the ischemic area is predisposed to the aggregation of erythrocytes. If endothelial damage occurs, localized hemoconcentration, erythrocythemia, and hyperproteinemia may result in aggregation, segmentation, and stasis of erythrocytes.

7. Systemic factors such as polycythemia, erythrocythemia, hemoconcentration, dehydration, and the introduction of high molecular weight substances, such as the plasma expanders PVP and dextran, into the circulating blood tend to increase the likelihood of cerebral infarction in ischemic areas.

The authors thank Mr. Peter Miller for his technical assistance in this study.

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Maple syrup disease

Investigations into the metabolic defect

John H. Menkes, M.D.

In 1954, Menkes, Hurst, and Craig[1] reported 4 cases of a familial cerebrodegenerative disease, characterized by the excretion of urine possessing a maple syrup–like odor. Since then, 7 further cases appearing in 4 unrelated families have either been reported or brought to my attention.[2–4] All patients have been products of normal pregnancies and deliveries. They appeared quite well until the latter part of the first week of life, when they would stop nursing, lose their Moro reflex, and begin excreting their characteristic urine. Within a day or so, a state of decerebrate rigidity with marked but intermittent opisthotonus ensued. Other symptoms included respiratory irregularities causing cyanotic episodes, and occasional generalized seizures. In 10 out of 11 cases, this condition was fatal, death occurring between the ages of 11 days and 20 months. The usual diagnostic procedures have been of little help. Electroencephalograms done in 2 of the reported cases showed multifocal spike discharges, very similar to records obtained in infantile spasms. A pneumoencephalogram performed on 1 of our patients[1] was said to have shown slight cortical atrophy. Autopsies were done in 2 cases; 1 of these patients died at 11 days and the other at 14 days of age. Both brains were somewhat edematous, without any evidence of either white or gray matter degeneration.

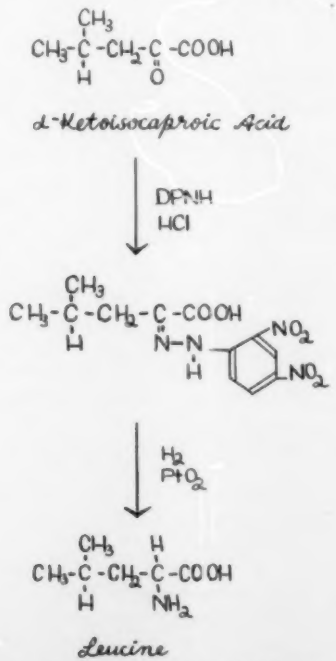

Fig. 1. Conversion of alpha-ketoisocaproic acid to leucine

Extensive investigations of urines obtained from patient G.B., reported already in detail,[5] led to the isolation of alpha-ketoisocaproic acid (subsequently referred to as KICA), in the form of its 2,4-dinitrophenylhydrazone derivative (DNPH). The structure of this derivative and the presence of smaller amounts of alpha-keto acids, corresponding to valine and isoleucine (alpha-ketoisovaleric acid—KIVA, and alpha-keto-beta-methyl-n-valeric acid–KMVA) were confirmed by reconverting each keto acid to its analogous amino acid by means of the reaction sequence in Figure 1.

The presence of these acids in urine led to one to suspect an impairment in the degradation of the branched chain amino acids—leucine, valine, and isoleucine—with the block perhaps being located at the site of oxidative decarboxylation of the alpha-keto acids (step 2, Fig. 2).

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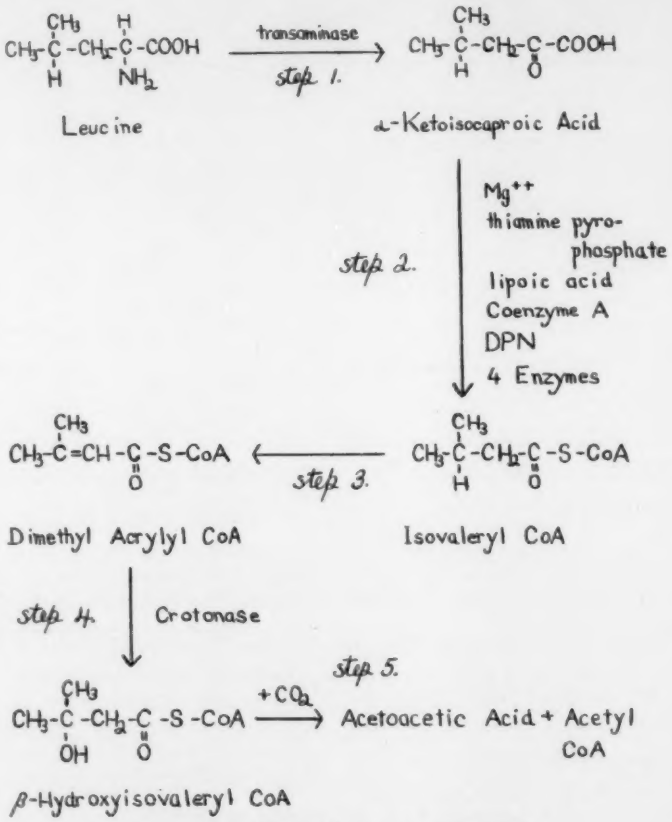

Fig. 2. Degradation of leucine in animal tissues

The urinary amino acid pattern in maple syrup disease was normal within the first few days following birth,[1] but column chromatography on later specimens taken from G.B. showed an elevation in the output of leucine, valine, isoleucine, and methionine.[4] While the excretion of the first 3 amino acids could easily be explained from the postulated defect, the methionine elevation was still unclarified.

Aside from determining the cause of the methionine excretion, other problems remained to be solved. First, an attempt was made to verify the site of metabolic block. Normal decarboxylation of alpha-ketoisocaproic acid leads to the formation of the coenzyme A derivative of isovaleric acid (IVA) (step 2, Fig. 2), which, in turn, splits off water to form the coenzyme A derivative of dimethylacrylic acid (DMAA) (step 3, Fig. 2). It seemed reasonable, therefore, to suppose that elevation of the tissue concentrations of either isovaleryl coenzyme A or dimethyl acrylyl coenzyme A would result in the presence in urine of their hydrolytic products, IVA and DMAA. Inasmuch as the degradative pathways of the branched chain amino acids diverge after step 4 (Fig. 2), it was not thought necessary to search for metabolites beyond that point.

Next, the nature of the maple syrup odor and its relationship to the metabolic defect had to be explained. Third, a brief investigation into the urinary acid excretion patterns of

TABLE 1

PAPER CHROMATOGRAPHY OF URINARY ACIDS

	Compound	*Rf*	*BPB*	*UV*	*DNPH*
Maple syrup urine, total acids	KICA+Acid A	0.65–.68	3+	+	3+
	KIVA	0.58	0	±	1+
	Acid B	0.53	2+	+	0
	Acid C	0.40	1+	+	0
	Acid D	0.35	1+	+	0
		0.02	4+	0	0
After keto acid precipitation	Acid A	0.66	3+	+	
	Acid B	0.54	2+	+	
	Acid C	0.40	1+	+	
	Acid D	0.33	1+	+	
Normal urine		0.47	1+	+	0
		0.34	1+	+	0
IVA (50 gamma)		0.65	3+	0	0
DMAA (50 gamma)		0.63	4+	+	0
KICA (50 gamma)		0.68	1+	+	4+

Solvent: Butanol, 100 parts; water, 15 parts; diethylamine, 1 part.
Descending chromatography on Whatman No. 40 paper.
Spots identified by bromphenol blue spray (BPB),[7] ultraviolet light absorption (UV), and 2,4-dinitrophneylhydrazine spray (DNPH).[8]
Equivalents to 0.02 cc. urine used in all cases.

some of the patients' relatives seemed worthwhile in order to uncover possible cases with partial metabolic block.

Finally, through correlation of all findings up to now, an attempt will be made to explain the catastrophic effects of this metabolic defect upon the central nervous system.

SEARCH FOR IVA AND DMAA

An initial survey of both the volatile and nonvolatile urinary acids was performed by means of paper chromatography in butanol-diethylamine and water.[6]

Urine (1 cc.) was acidified to *p*H 2 with sulfuric acid and extracted with three 5-cc. portions of ether. The ether extracts were shaken with 10% Na_2CO_3. The carbonate solution was acidified with sulfuric acid and reextracted with ether. The final volume was adjusted to 1 cc. An aliquot was treated with 2,4-dinitrophenylhydrazine (2% solution in 2N HCl), and the precipitated keto acids were centrifuged off.

From Table 1, it may be seen that, aside from the previously identified keto acids that reacted with DNPH spray, at least 4 other urinary acids were present in significant amounts. The spot with a chromotographic migration ratio (Rf) of 0.02 was due to the sulfuric acid present. None of these other compounds corresponded to IVA, although acid A, with an Rf of 0.66 and ultraviolet light absorption, could possibly have been DMAA.

Additional acids were not demonstrated by 2-dimensional chromatography using butanol-diethylamine and butanol-ammonia as solvents.

In order to isolate these 4 other compounds, tentatively termed acids A, B, C, and D in order of decreasing Rf's, and thus prove the absence of DMAA, silica-gel column chromatography was used. The procedure of Marvel and Rands[9] was followed, and elution of the acids from the column was accomplished with chloroform containing progressively higher concentrations of butanol.

The elution curve obtained from 25 cc. of urine from patient C.O'C. is presented in Figure 3, together with a control curve from R.L., aged 7 years and hospitalized with bronchial asthma. G.B., another infant with maple syrup disease, showed an essentially similar curve, containing somewhat lesser amounts of each of the acids. The elution pattern on J.J.H., one of the first 4 cases presented,[1] was also similar.

Approximately 0.07 mEq. of acid A, which was present in the initial paper chromatography and could have been DMAA, was found in

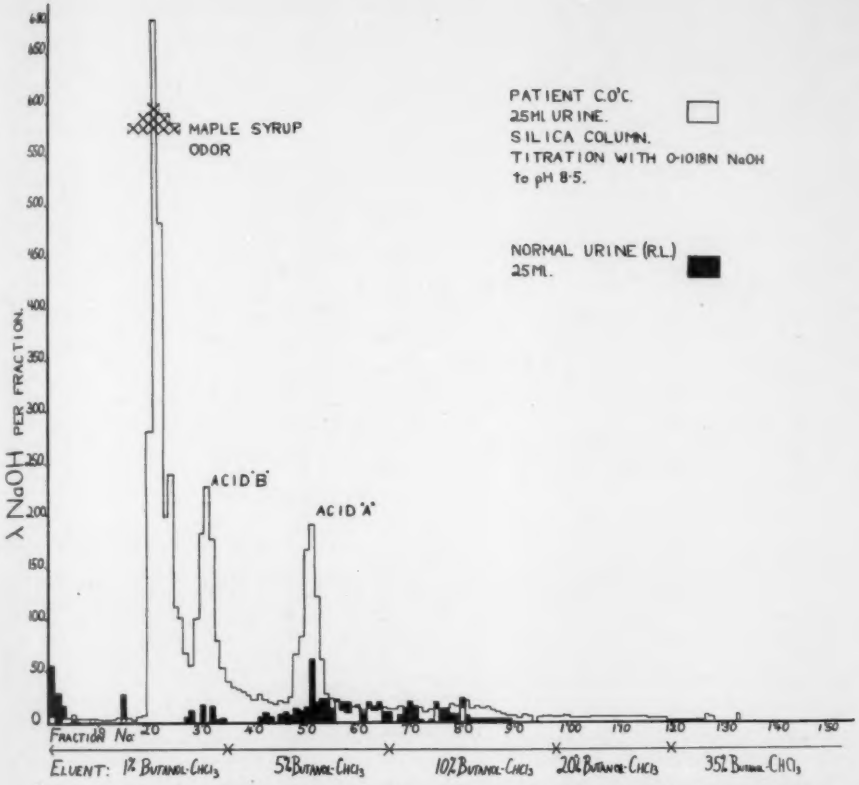

Fig. 3. Silica column chromatography of maple syrup urine (patient C. O'C.) compared with a normal control (R.L.). Besides the keto acids present in tubes 20 to 28, 2 other acidic compounds are found. Acid A is present in tubes 48 to 53 and acid B, in tubes 29 to 33. The maple syrup odor was found in tubes 19 to 23, thus partially coinciding with some of the alpha keto acids.

tubes 47 through 53 and was reidentified by paper chromatography. Its isolation was performed by evaporation of the chloroform-butanol solvent. The compound was purified by dissolving it in 10% Na_2CO_3 and reprecipitating it by the addition of HCl. About 3 mg. of white needles was obtained. Its melting point—210-212° C. (uncorrected)—is totally different from that of DMAA (m.p.: 70°).

From tubes 29 through 33, approximately 0.09 mEq. of acid B could be isolated. Further studies on the identity of these compounds will be presented in a subsequent paper.

Tubes 20 through 27 contained the previously identified alpha-keto acids (KIVA, KICA, and KMVA), which were identified by paper chromatography of their DNPH derivatives in parallel with the hydrazones prepared from authentic KICA and KIVA. A fourth keto acid, DNPH, possessing an Rf lower than these 3, was also detected in small quantities. Inasmuch as catalytic reduction of this DNPH resulted in the formation of an amino acid with the chromatographic properties of alanine, it seemed likely that the keto acid was pyruvic acid. The maple syrup odor was located in tubes 19 through 23 and thus was partially eluted with the alpha-keto acids.

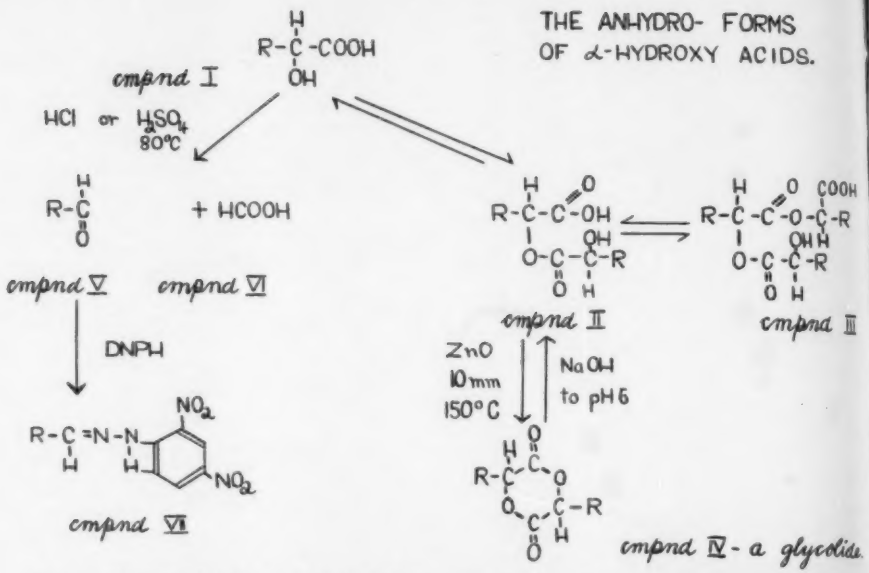

Fig. 4. The "anhydro" forms of alpha hydroxy acids. Compound I—Alpha hydroxy acid. Compound II—Product formed by the esterification of the acid group of 1 molecule and the hydroxy group of another. Compound III—Compound formed by esterification of 3 molecules of alpha hydroxy acid. Compound IV—A glycolide, a cyclic diester. Compounds V and VI—Cleavage of alpha hydroxy acids results in formation of an aldehyde and formic acid. Compound VII—The 2,4-dinitrophenylhydrazone derivative of the aldehyde

From the above data, the presence of at least 4 other urinary acids, none of which were direct degradation products of leucine, seemed evident.

IDENTIFICATION OF MAPLE SYRUP SUBSTANCE

Isolation and identification of the compound responsible for the characteristic maple syrup odor presented a more difficult problem, mainly because of the small quantities in which it was excreted.

Smith and Strang reported the occurrence of a cerebral degenerative disease in an infant, which was associated with the urinary excretion of large amounts of phenylalanine, tyrosine, methionine, and leucine, together with phenylpyruvic and alpha-hydroxybutyric acids.[10,11] This infant's urine also had a rather peculiar odor, attributed by the authors to the presence of the glycolide of alpha-hydroxybutyric acid (compound IV in Fig. 4, $R = C_2H_5$). Upon comparison with a urine specimen from an infant with maple syrup disease (G.B.), the urines were found to have both identical odors and similiar chromatographic patterns. Alpha-hydroxybutyric acid (HBA), however, was absent from G.B.'s urine.[12]

The possibility that the compound responsible for the odor was a glycolide of another alpha-hydroxy acid, particularly of alpha-hydroxyisocaproic acid (HICA), still remained, and a more rigorous structure proof had to be initiated.

Pure HBA is very hygroscopic and in water solution is present in equilibrium with its "anhydride" (compound II, Fig. 4, $R = C_2H_5$).[13,14] Thus, when the impure acid is chromatographed, 3 or even 4 spots may appear on the paper (Table 2).

Since all of these polymers of HBA are esters, the hydroxylamine colorimetric determination specific for esters and lactones[15] was performed on tube 21 (Fig. 3); 2.8 μEq. of an

ester was found to be present. This is equivalent to 0.48 mg. of compound IV or compound II (Fig. 4, $R = C_2H_5$).

Since alpha-hydroxy acids can be cleaved to aldehydes containing 1 less carbon atom,[16] identification of the hydroxy acid by its conversion to compounds V and VI (Fig. 4) seemed feasible. The aldehyde produced (compound V, Fig. 4, $R = C_2H_5$) could then be identified by its DNPH derivative (compound VII, Fig. 4, $R = C_2H_5$). Because of the small quantitites of material available, a concentrated solution of H_2SO_4 or HCl was used for the conversion of the hydroxy acid to the aldehyde in preference to the more commonly employed lead tetraacetate oxidation.

The ester responsible for the maple syrup odor was separated from the alpha-keto acids by repeated extractions of the original urine (patient C.O'C.) with n-hexane, into which the keto acids are insoluble. The resulting extract was passed through a silica-gel column and eluted progressively with hexane, hexane-chloroform, chloroform, and chloroform containing 1% butanol.

Alkali titration of the tubes containing the maple syrup odor showed the presence of a total of 1.6 μEq. of an acid. These fractions were now combined, brought to a *p*H of 12 with 2N NaOH, and heated on a steambath with an attached reflux condenser for two hours; 1 cc. of concentrated H_2SO_4 was then added. The mixture was heated for two hours more and then allowed to stand overnight at room temperature. DNPH (0.5 cc. of a 1% solution in 2N HCl) was added, and the solution became cloudy. The hydrazones produced were extracted with several portions of chloroform. Using a similar method on the urine of patients G.B., a pure sample of a hydrazone could be isolated. This was found to have a melting point of 146 to 147° C. (uncorrected). Propionaldehyde DNPH, the expected product from the hydrolysis of alpha-hydroxybutyric acid, has a melting point variously reported as 150 and 153 to 154° C. An ultraviolet spectrum in absolute alcohol showed the unknown DNPH to have a maximum at 354 mμ., indicating it to be a derivative of an aldehyde.[17]

Further proof of the nature of the aldehydic oxidation product was afforded by chromatographing the hydrolysis mixture with the authentic DNPH of propionaldehyde (m.p.: 151 to 153°, uncorrected) (Table 3).

TABLE 2

PAPER CHROMATOGRAPHY OF ALPHA-HYDROXYBUTYRIC ACIDS

	Compound	*Rf*
Acids from maple syrup urine	Acid A+KICA+ODOR	0.65
	Acid B	0.53
	Acids C+D	0.38
	Inorganic acids	0.02
	HBA (pure)	0.42
	HBA (impure)	0.42
		0.57
		0.67
	Alpha-hydroxy-isocaproic acid	0.61

Solvents: Isopropanol, 200 parts; conc. ammonium hydroxide, 10 parts; water, 20 parts. Descending chromatography on Whatman No. 40 paper. Spots identified by application of Nessler's reagent.

Authentic HBA, upon hydrolysis to propionaldehyde, gave a similar mixture of dinitrophenylhydrazones. The other products were probably due to autocondensation of propionaldehyde in the presence of a strong acid. Isovaleraldhyde DNPH, the product expected from the cleavage of alpha-hydroxyisocaproic acid, has an Rf greater than that of butyraldehyde DNPH in the solvents employed[18] and a melting point of 123° C.

To show that formic acid was also produced by this cleavage, a part of the mixture was subjected to paper chromatography in parallel with authentic formic acid (Table 4).

At this point, synthesis of the compound responsible for the maple syrup odor, diethyl

TABLE 3

CHROMATOGRAPHY OF THE DNPH's OF THE OXIDATION PRODUCTS OF MAPLE SYRUP SUBSTANCE

	Rf
Patient C. O'C.:	0.11
	0.46
	0.70
	0.79
Patient G.B.:	
Purified compound (m.p.: 146°–147°)	0.79
Propionaldehyde DNPH	0.79
Butyraldehyde DNPH	0.84

Solvents: Methanol, 150 parts; n-hexane, 150 parts. Descending chromatography on Whatman No. 40 paper. Spots detected by their intrinsic color and under UV light.

TABLE 4

PAPER CHROMATOGRAPHY OF ACID OXIDATION PRODUCTS OF MAPLE SYRUP SUBSTANCE

	$AgNO_3$	Rf
Oxidation mixture Patient G.B.	Black	0.31
Formic acid	Black	0.32
Glycolic acid	Yellow	0.21

Solvents: Butanol, 100 parts; water, 15 parts; diethylamine, 1 part. Descending chromatography on Whatman No. 40 paper. Spots identified by hanging in atmosphere of ammonia vapors and then treating with Nessler's reagent. Formic acid distinguished from acetic acid by its blackening reaction with ammoniacal $AgNO_3$.[19]

glycolide (compound IV, Fig. 4, $R=C_2H_5$), was undertaken. The method employed was that described by Dietzel and Krug[20] for the preparation of lactide, the lactic acid analogue of compound IV (Fig. 4, $R=CH_3$).

From 6.5 gm. of HBA, 1.5 gm. of diethyl glycolide was obtained, having a melting point of approximately 15 to 20° C. The reported melting point of diethyl glycolide is 21 to 22°.[21]

When diethyl glycolide was dissolved in water, slow hydrolysis to compound II (Fig. 4, $R=C_2H_5$) occurred. This hydrolysis was quite slow as long as the *p*H of the solution remained between 3 and 4. At a *p*H higher than 6, the hydrolysis accelerated markedly, so that a titration with alkali became possible. This resulted in an equivalent weight of 170.9. The calculated molecular weight of diethyl glycolide is 172.2.

This compound, which Smith and Strang[10] believed to be responsible for the maple syrup odor, possesses a peculiar, disagreeable, acrolein-like smell, and only after it stands for some time in air at room temperature does an intense maple syrup odor develop. The paper chromatographic behavior of diethyl glycolide was also quite unlike that of the product responsible for the maple syrup odor of C.O.C.'s urine. Thus, one is forced to conclude that this odor is not due to diethyl glycolide itself but rather to a decomposition product, such as compound II or perhaps a mixture of compounds II and III or even higher polymers (Fig. 4, $R=C_2H_5$).

URINARY ACIDS IN RELATIVES OF PATIENTS WITH MAPLE SYRUP DISEASE

In order to determine whether a partial metabolic block in the degradation of alpha-keto acids can be found in relatives of patients with maple syrup disease, the urines of 5 family members of 2 unrelated patients, G.B. and Baby Boy S., were chromatographed to show the presence of total acids and keto acids.

Urine samples were obtained from Father B., Mother B., and Sister B., members of G.B.'s family, and from Mother and Sister S., members of a family in which 2 boys died with what was reported by their physician as typical cases of maple syrup disease.[22]

The paper chromatography for total urinary acids is shown in Table 5. Sister S., and probably also Mother S., excreted an abnormal acid with an Rf of 0.65. This compound was isolated and identified, by means of its melting point, ultraviolet spectrum, equivalent weight, acid dissociation constant (*p*Ka), and by mixed melting point with an authentic sample, as being benzoic acid. The significance of the

TABLE 5

PAPER CHROMATOGRAPHY OF URINARY ACIDS IN RELATIVES OF PATIENTS WITH MAPLE SYRUP DISEASE

Subject	*Patient* G.B.	*Mother* S.	*Sister* S.	*Father* B.	*Mother* B.	*Sister* B.	*Normals*
Rf values	0.83 3+	0.84 tr.					
	0.78 tr.						
	0.68 2+	0.65 2+	0.65 4+	0.62 1+	0.66 tr.	0.66 tr.	
		0.53 tr.					0.53 1+
	0.44 1+	0.43 4+	0.40 3+	0.42 1+	0.42 1+	0.41 1+	0.41 1+
		0.24 tr.					

Equivalents of 0.02 cc. of urine applied.

Solvent: Isopropanol, 200 parts; concentrated ammonium hydroxide, 10 parts; water, 20 parts. Descending chromatography on Whatman No. 40 paper. Spots identified by treatment with Nessler's reagent. The values for normals represent the average locations obtained from several such determinations.

urinary benzoic acid is unknown at this time, and further studies to exclude its dietary origin are still required.

The alpha-keto acid excretions were essentially normal. Father B. excreted a small amount of alpha-ketoisocaproic acid. This, however, contrary to previous studies,[23] has been a fairly usual finding in normal urines.[24]

DISCUSSION

The absence of IVA and DMAA in the presence of increased urinary excretion of KICA, KIVA, and KMVA, together with their respective amino acid analogues, suggests that the site of degradative arrest occurs at the stage of oxidative decarboxylation of the alpha-keto acids. The presence of the polymer of HBA, the substance responsible for the maple syrup odor, could be explained by postulating its formation from alpha-ketobutyric acid, the oxidative decarbxylation of which might also be impaired. The latter is a known degradation product of methionine, the excretion of which was increased in patient G. B.[4] (Fig. 5).

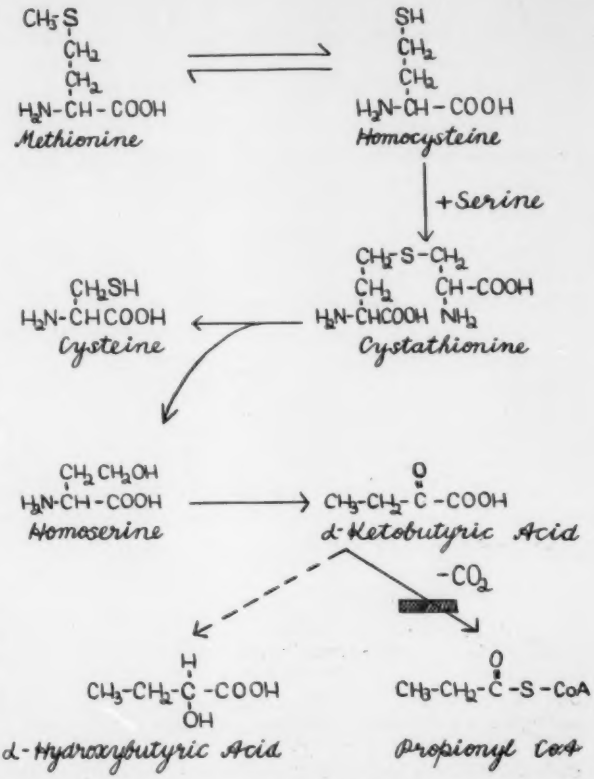

Fig. 5. Metabolic conversion of methionine. Alpha-hydroxybutyric acid and its polymers could arise through the production of alpha-ketobutyric acid, the oxidative of which decarboxylation to propionyl coenzyme A is slowed or arrested.

Various causes for the interruption of oxidative decarboxylation might be postulated. Normally, the reaction proceeds through the series of steps outlined in Figure 6. This figure depicts the most likely mechanism as derived from the evidence available at this time.[25–27] It is known to be applicable for the decarboxylation of pyruvic acid and probably also for alpha-ketoglutaric and alpha-ketobutyric acids. The reaction is known to require the presence of thiamine pyrophosphate, magnesium, coenzyme A, DPNH, and lipoic acid, the last probably both in a free and protein-bound state.[28] In addition, as many as 4 separate enzymes may be needed.[25]

In order to postulate the deficiency of 1 specific enzyme involved in 1 of the above steps as the cause for the accumulation of the various keto acids, one should first be able to show that KICA, KIVA, KMVA, and, perhaps, alpha-ketobutyrate utilize common enzymes in their oxidative decarboxylation. At the present time, there is no experimental evidence to support such an assumption.

Another possibility is the deficiency of 1 of the coenzymes partaking in the reaction. A lack of coenzyme A or DPNH seems unlikely because of the numerous processes requiring these 2 substances. Thiamine deficiency on a purely dietary basis seems fairly well excluded,

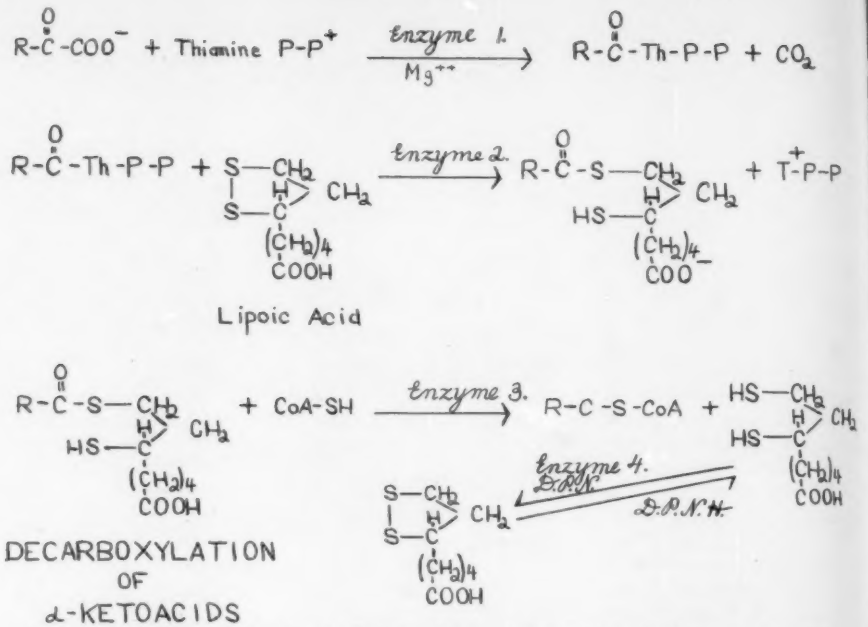

Fig. 6. Proposed mechanism for the decarboxylation of alpha-keto acids. Enzyme 4 has been isolated in a crystalline state. Enzyme 1 may be a lipoic acid–protein complex.

but the presence of a thiamine antagonist resulting from a metabolic derangement at some other site possesses some plausibility, and studies have been set up to test this hypothesis. The absence of lipoic acid or failure to form a lipoic acid–protein complex also must be ruled out. Under all these circumstances, an accumulation of other alpha-keto acids, most particularly pyruvic and alpha-ketoglutaric acids, would be expected. This, however, was not found to be the case. Alpha-ketoglutaric acid was excreted in normal amounts, and pyruvic acid, perhaps due to decomposition during storage of the urine, in small quantities only.

Finally, it is also possible that the accumulation of KICA resulting from a deficiency in a KICA specific enzyme will result in complete or partial inhibition of the oxidative decarboxylation of those keto acids found to be excreted in lesser quantities. This, considering the somewhat analogous situation in phenylketonuria, seems at present the most likely hypothesis.

To set up a rational plan of therapy for maple syrup disease in the absence of more definite knowledge as to the actual metabolic defect is difficult. In analogy with phenylketonuria, one could prepare a diet free of leucine.* Another method of treating these patients would be the administration of 1 of the coenzymes, such as lipoic acid, which is commercially available, or thiamine. In any case, therapy presumably would have to be instituted early in life in order to prevent irreversible central nervous system damage.

The reason why such a defect in oxidative decarboxylation causes central nervous system damage is, of course, unknown. Recent papers by Dunn and associates[29,30] raise an interesting possibility. These authors show that both alpha-hydroxyisocaproic acid and alpha-hydroxyisovaleric acid are essential in the production of cerebronic acids in Lactobacillus casei. These long-chain alpha-hydroxy acids

*This has now been attempted in 2 children with at least partial success in arresting the neurologic symptoms in 1 case.

have the same configuration in both microorganisms and the mammalian brain, and, thus, their methods of synthesis may well be identical. It can easily be assumed that high KICA and KIVA levels interfere with cerebronic acid synthesis in the growing brain and thus cause the observed dysfunction.

SUMMARY

1. The clinical picture of maple syrup disease, a cerebral degenerative condition with its onset in the first week of life and rapid progression to a decerebrate stage, is described.

2. Urine excreted by patients with this condition has an odor strongly reminiscent of maple syrup.

3. An accumulation of 3 keto acids—alpha-ketoisocaproic acid, alpha-ketoisovaleric acid, and alpha-keto-beta-methyl-n-valeric acid—together with the absence of other metabolites along the degradative pathway of leucine suggests that oxidative decarboxylation of the alpha-keto acids is blocked in this condition.

4. A polymer of alpha-hydroxybutyric acid is believed to be responsible for the maple syrup odor.

5. No partial block in oxidative decarboxylation could be demonstrated in relatives of affected children.

6. Various possibilities as to the specific cause for the metabolic arrest have been examined, and it has been suggested that high tissue levels of alpha-ketoisocaproic acid inhibit the synthesis of cerebronic acids.

The author wishes to thank Drs. Sidney Carter, Sara Ginsburg, H. H. Merritt, Rustin McIntosh, D. B. Sprinson, and Irwin B. Wilson for their valuable assistance in preparing this paper; Prof. Alan Moncrieff, Hospital for Sick Children, London, for the urine sample from patient C. O'C.; and Dr. J. Dancis, New York University, for the urine sample from patient G.B. The authentic KICA was obtained from the K. and K. Laboratories, New York City, and the authentic KIVA, from the Sigma Chemical Company, St. Louis.

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CASE REPORT

Occlusion of the third ventricle by tortuous, bulbous, calcified basilar artery

Hendrik J. Svien, M.D., and Luigi Peserico, M.D.

A LONG BASILAR ARTERY occasionally may cause an indentation in the bottom of the third ventricle, particularly if the elongated artery is rigid and tortuous as a result of arteriosclerosis. This was reported upon by Lindgren[1] in 1950 and Sjögren[2] in 1953. In 1954 Greitz and Löfstedt[3] reported on 5 cases of such deformation of the floor of the third ventricle.

REPORT OF CASE

A married man, 59 years old, registered at the Mayo Clinic on February 12, 1957, because of marked mental disorientation. He apparently had been in reasonably good health until December 1956, when he suffered what was called a "stroke." He felt ill, lay down on the ground, and vomited. He was not paralyzed after this episode, however. At this time, hypertension was discovered. Attempts at treatment with drugs failed because of lack of cooperation on the part of the patient. A month before his admission, edema of the legs developed and became progressive to a rather marked degree. Examination by the patient's local physician disclosed auricular fibrillation. The patient was hospitalized in his home city two weeks before admission to the clinic, and digitalis and diuretic agents rid him of much of the edema.

Apparently, the patient had experienced no neurologic symptoms until about mid-December of 1956. At that time, it was noted that he was becoming confused. He became disoriented for several hours and then seemingly recovered orientation completely. However, in the ensuing three or four weeks, he had repeated episodes of confusion. The patient was confused as to time and place and was unable to carry rather simple instructions. He experienced no headaches or convulsions. While in the hospital under treatment for heart failure, he became markedly disoriented and drowsy, and this condition had persisted. No other deficiencies referable to the central nervous system were noted during hospitalization.

General physical examination revealed the blood pressure to be 210/170 mm. Hg, with an irregular pulse rate that averaged about 72 beats per minute. Results of the remainder of the general physical examination were essentially negative. Cardiac consultation revealed auricular fibrillation, with minimal cardiac enlargement. A diagnosis of hypertensive cardiovascular disease, with previous failure presently compensated, was made. Roentgenologic examination of the thorax disclosed a Ghon complex, left ventricular cardiac enlargement, and torsion of the aorta. Grade 3 albuminuria, grade 2 erythruria, and an occasional leukocyte were found. The value for urea was 51 mg. per 100 cc. of blood.

The impression of the medical consultant was that it was unlikely that the mental condition of the patient was caused by drugs or by the hypertension in itself. The question of some primary disturbance of the central nervous system was raised. Roentgenologic examination of the skull revealed a curvilinear strand of calcification situated above and slightly to the left of the sella turcica, with erosion of the left anterior clinoid process (Fig. 1). Hypertensive narrowing, grade 2, of the retinal arterioles, with focal constrictions of

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grade 2 and sclerosis of grade 2, and 1 small retinal hemorrhage were found.

At neurologic examination, the patient was found to be rather stuporous. He was facetious in varying degrees throughout the examination and was disoriented in respect to time and place. No disturbance of the cranial nerves or motor or sensory function was noted.

An electroencephalographic study revealed generalized dysrhythmia of grade 2. It was felt that this recording indicated the possibility of a disturbance in the vicinity of the third ventricle or hydrocephalus at the third ventricle. Because of the calcification noted in the roentgenograms of the skull and the patient's mental status, as well as the internist's opinion that the hypertensive disease probably was not responsible for the patient's disorientation, ventriculography was advised.

Ventriculographic examination was carried out on February 18, 1957, and revealed dilation of the lateral ventricles caused by a partially calcified, space-occupying lesion deforming the anteroinferior aspect of the third ventricle (Fig. 2). The mass was noted to be in the midline and to extend over to either side. Examination of the ventricular fluid demonstrated 1 lymphocyte and 7 erythrocytes per cubic millimeter of fluid, and the protein content of the cerebrospinal fluid was 75 mg. per 100 cc.

During the period of observation, the patient's condition deteriorated progressively. Results of the roentgenogram of the skull and the ventriculogram suggested that an aneurysm might be present. Consequently, bilateral carotid arteriographic examination was done after the ventriculogram had been made. This study indicated that the carotid siphon on each side was elevated by what appeared to be a mass projecting to each side of the midline in the sellar region (Fig. 3a and b). Nothing suggested a cerebral aneurysm.

It was felt that the patient might have a cystic lesion, possibly a craniopharyngioma, in the region of the third ventricle and that such a lesion might be responsible for his symptoms. Right transfrontal craniotomy was carried out. The optic nerves and chiasm were explored, but nothing abnormal was noted in this region. A transcortical incision was made in the right frontal lobe at the coordinate of the foramen

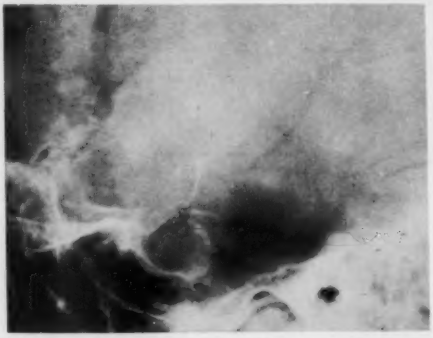

Fig. 1. A curvilinear strand of calcification is disclosed above the sella turcica.

of Monro, and the right lateral ventricle was entered. The foramen of Monro was identified and appeared to be normal. Nothing bulged into it. Next, the foramen of Monro was enlarged by sectioning the fornix anteriorly, and the region of the third ventricle was inspected. Nothing abnormal could be seen.

It was concluded that, if a tumor was present, it was lying underneath the third ventricle, posterior to the chiasma, in a region inaccessible to surgery. The patient did poorly after the operation and died on the next day.

At necropsy, the brain was seen to be markedly edematous. The convolutions were

Fig. 2. Ventriculogram shows dilation of the lateral ventricles and indentation of the floor of the third ventricle.

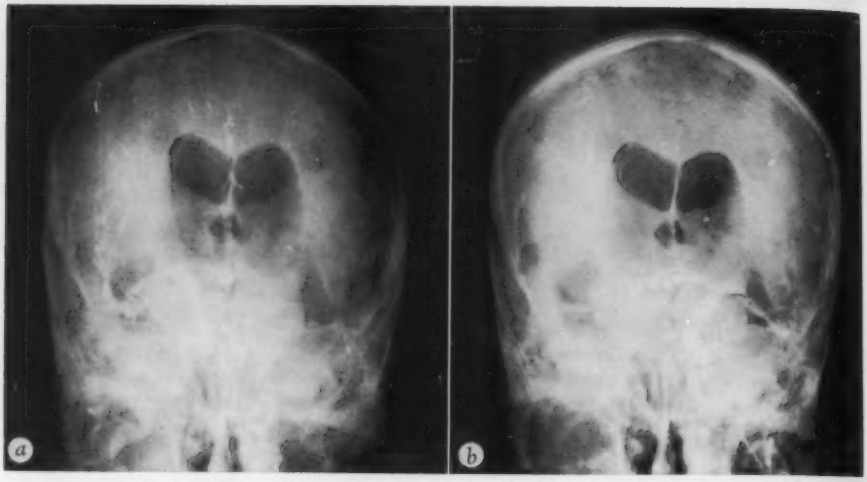

Fig. 3. Right [a] and left [b] carotid angiogram. showing elevation of the carotid siphon on each side

narrowed, and the gyri were flattened. When the brain was removed, the basilar artery was observed to be long, tortuous, and dilated. The walls of this vessel were thickened and calcified. Tumor tissue was not found. The necropsy data made it apparent that the basilar artery had brought about elevation of the floor of the third ventricle and had produced the roentgenologic findings.

COMMENT

The basilar artery may extend considerably above the posterior clinoid processes. The relationship of this vessel to the floor of the third ventricle, however, seems to be less variable. Some years ago, this relationship was determined in vivo by comparison of the findings in pneumograms and vertebral angiograms when both examinations were performed on the same patient and at necropsy by filling the third ventricle with air and the vertebral artery with contrast medium.[3] At that time, the basilar bifurcation was found to have an almost constant position immediately behind the posterior part of the hypothalamus, so that the distance of this bifurcation from the nearest part of the third ventricle varies between 0 and 6 mm. The size of the basilar artery varies considerably, but it seems likely that pathologic changes, such as arteriosclerosis and high blood pressure, are necessary to cause ectasia of the artery to such a degree that the third ventricle becomes indented. In the cases reported by Greitz and Löfstedt,[3] the clinical and roentgenologic signs of advanced arteriosclerosis were present. The blood pressure was considerably increased, the systolic pressure varying between 200 and 240 mm. Hg. In our case, arteriosclerosis of the basilar artery was a prominent feature and the blood pressure was 210/170 mm. Hg.

The indentation produced on the floor of the third ventricle by an ectatic basilar artery must be distinguished from the impression caused by tumors of the brain stem, tumors arising from the sella turcica, or aneurysms. In such a situation, vertebral angiographic examination provides the best form of investigation; however, this procedure is associated with considerable risk in patients who have a basilar artery affected by arteriosclerotic changes.

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Autonomic regulatory mechanism in human spinal cord

I. Blood pressure responses and results of square wave stimulation in patients subjected to spinothalamic tractotomy

D. M. Perese, M.D., and Robert O. Bauer, M.D.*

IN THE CAT, some autonomic fibers originate in the lateral hypothalamic area, run through the tegmentum of the midbrain and pons, traverse the lateral part of the reticular formation of the medulla, and descend in the ventrolateral column of the spinal cord.[13] Stimulation of the lateral reticular formation in the medulla and the periventricular area in the pons produces vasopressor reactions.[15] These pressor pathways, after partial decussation in the brain stem, descend in the ventrolateral column of the spinal cord.[16]

Earlier anatomic studies on patients who had undergone cervical sympathectomies indicate that the cells in the lateral horns of the spinal cord show marked retrograde degeneration.[3–7] These observations are supported by investigations of the alteration of the sweat mechanism after vascular lesions of the pons, medulla, and cervical spinal cord[12] and tractotomies of the upper thoracic spinal cord.[10]

A more serious effect of human chordotomies, however, appears to be the lowering of the blood pressure, presumably as the result of damage inflicted to the cells of the intermediolateral column during spinothalamic tractotomies.[3,8,9,11]

In man, White[17] has initiated experimental stimulation along the autonomic descending pathways, as performed previously in animals. Using 3- to 4-volt, 60-cycle alternating current through a bipolar electrode, he stimulated the human hypothalamus and observed abrupt acceleration of the heart and a rise in blood pressure comparable to that reported in experimental animals.[1,2,10]

We have observed vasomotor changes in a large number of patients undergoing spinal tractotomies that extended into the cells of the intermediolateral column.[14] In order to localize the autonomic area and avoid complete destruction of the fibers and cells, the spinal cord was stimulated at various depths during surgery. The results of our study form the basis of this report.

MATERIAL AND METHODS

Patients undergoing chordotomies in the cervical or thoracic regions of the spinal cord for the relief of pain caused by advanced malignant disease were prepared as follows: Immediately after endotracheal intubation of the conscious patient, a No. 18 or 14 thin-walled needle was introduced into the right brachial artery by percutaneous puncture and a polyethylene catheter of appropriate diameter was passed through the needle into the vessel. The catheter tip was advanced to the subclavian artery. Arterial pressure was recorded from the catheter by a Stathum R23D strain gauge and a model 150 4-channel Sanborn direct writing recorder. The strain gauge was standardized periodically, about every thirty minutes, against a mercury manometer. The catheter was flushed with 0.5 to 1 cc. of heparinized physiologic sodium chloride solution to preclude the damping effect of catheter clots on arterial pressure recordings. Then the patient was positioned on the operating table, and general anesthesia was induced with meperidine hydrochloride, nitrous oxide, and oxygen. The chordotomy was then performed.

Our technic of tractotomy included in the

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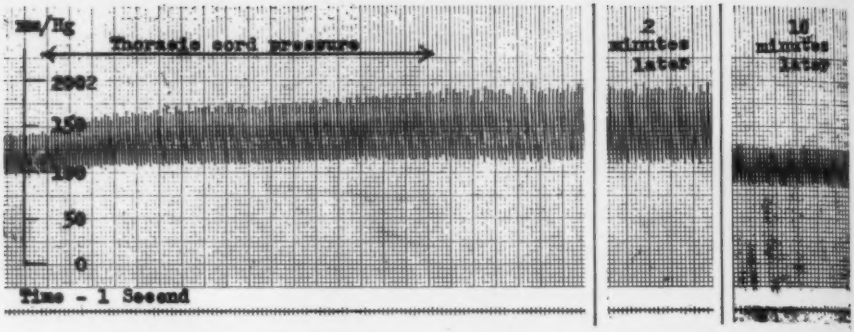

Fig. 1. Pressure on the exposed portion of the thoracic spinal cord produced a prolonged systemic arterial blood pressure rise. Pressure was applied during the time indicated by horizontal line (eighty-six seconds). Less profound effects were observed when a cottonoid paddy was placed under the nerve root or the electrode was pushed through the intact pia into the spinal cord.

section a part of the cells in the intermediolateral column, so as to achieve interruption of the visceral pain impulses. The extent of the incision into the cells of the intermediolateral column was determined by the drop of the peripheral blood pressure that followed the tractotomy. Marked hypotonia was undesirable because of the risk of uncontrollable and irreversible shock.[14]

After the blood pressure recording became stabilized, stimulation of the cells of the intermediolateral column was begun. A bipolar Grass stimulator having an air gap of about 1 mm. was used. The electrode, 5 mm. in length, was insulated except for less than 1 mm. of the tip. The tip was bent 90° to the axis of the handle, thus permitting its use in the human spinal cord within the restrictions of safe surgical exposure. The stimulation factors were as follows: 60- or 90-cycle, 1.5- to 10-volt, 100-μsec., biphasic alternating current produced by a Grass S-4-BD stimulator. Duration of the stimulus was variable. The stimulation in individual patients is described separately and tabulated in the table.

RESULTS

Case 1. M.W., a 69-year-old woman who had had bilateral chordotomy at C6 level two years earlier, on May 5, 1958, underwent a right lateral chordotomy at T1 level to section those fibers spared during the first operation. The width of the spinal cord was 8.5 mm., and the depth of the cut at the level of the dentate ligaments was 4 mm. Initial blood pressure in the subclavian artery before chordotomy was 110/80 mm. Hg. Blood pressure elevations indicated that the spinal cord was easily affected by manipulations such as traction on the posterior roots, gentle squeezing of the cord during placement of a cotton paddy under the anterior nerve root (Fig. 1), and irrigation of the spinal cord.

Stimulation with bipolar electrodes at a depth of 4 mm. slightly cephalad to the chordotomy incision produced no change in blood pressure on 2 occasions. However, caudad stimulation elevated the blood pressure from 125/90 to 150/100 mm. Hg for eight minutes. At the end of the sixth minute, blood pressure was 160/98. Caudad stimulation was repeated after extension of the tractotomy with more profound response. Following the second caudad stimulation, blood pressure rose to 225/125 mm. Hg and stayed at this level for ten minutes. Declining gradually, it stabilized at 150/90 ten minutes later (see table and Figure 2).

Case 2. L.S., a 64-year-old man, had the first stage of a bilateral thoracic chordotomy in April 1958. The second operation was performed at T1 level on July 16. The width of the spinal cord was 9 mm., and the depth of the cut at the level of the dentate ligaments was 4 mm. This cut was shorter than the usual chordotomy incision because we feared lowering the patient's blood pressure dramatically; the initial pressure of 100/87 rose to 115/100 mm. Hg during manipulation of the cord just before the tractotomy. After tractotomy, the blood pressure fell to 90/78 mm. Hg, where it stabilized. The bipolar electrode was placed 4 mm. deep in the cord at the dentate ligament level. With 60-cycle, 3-volt, and 100-μsec. biphasic alternating current, a ten-second stimulus elevated the blood pressure from 87/62 to 140/90 mm. Hg within forty seconds. This was repeated twice cau-

ARTERIAL BLOOD PRESSURE RESPONSES TO SPINAL CORD STIMULATION AFTER TRACTOTOMY

Case No.	Sex	Age	Chordotomy Level	Chordotomy Side	Blood pressure: Before: Cuff	Blood pressure: Before: Catheter	Blood pressure: Cord stimulation: Above cut catheter	Blood pressure: Cord stimulation: Below cut: Cuff	Blood pressure: Cord stimulation: Below cut: Catheter	Time	Duration electrical stimulus Sec.	Notes
1	F	69	T1	Right	110/80*	125/ 90*		112/ 80	125/ 90	10:49	100	All stim. 10 volts
					90/76	115/ 85	120/ 85			11:25:45	120	
					80/60	125/ 92	125/ 90			11:50	110	Extended unilateral cut
					100/80	155/103		140/100	225/125	11:55	135	Sustained rise 10 minutes
					112/90	150/ 90				12:15		
					84/60	120/ 85				13:20		Patient awake
2	M	64	T1	Bilateral	70/36*	98/ 87*				10:30		
					76/40	90/ 78	90/ 78			10:35		Cord cut (left) T1
						100/ 68	80/ 55			10:40	5	
						94/ 78	80/ 55			10:45	5	
						90/ 80	80/ 50			10:55	10	
						87/ 62		120/ 70	140/ 90	11:00	10	
						100/ 70		120/ 50	130/ 80	11:10	10	Stimulus on rt. T1
						100/ 68			125/ 75	11:15	10	
						125/ 90				12:15		Patient awake
3	F	75	C1	Left		290/170	290/180			15:32	10	
			C3	Left	124/90*	280/175*	280/170			15:40	10	
						290/170	290/170			15:45	10	
						250/150			280/170	15:50	10	
						260/155			280/180	15:53	10	
						280/120				16:30		End operation
4	F	56	C2	Left	124/90*	175/ 95*				11:45		
						110/ 95	110/ 95			12:30	5	
						115/ 95	115/ 95			12:35	5	
						120/100	120/100			12:40	5	
						125/100	125/100			12:45	40	
						125/100			135/110	13:01	60	
						125/100			140/115	13:06	60	
						150/115				14:26		End operation Patient awake

*Comparative arterial blood pressures in same arm before cord section

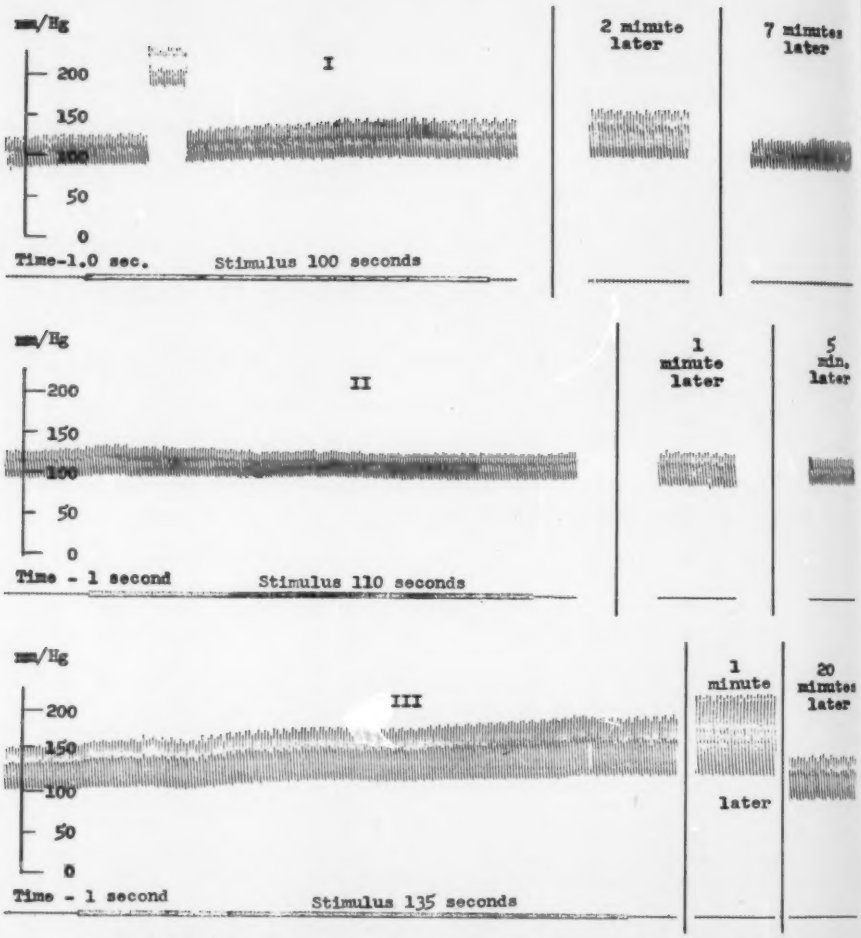

Fig. 2. Arterial blood pressure responses to spinal cord stimulation after tractotomy at T1 (right side). Electrical stimulation was accomplished with 10-volt, 60-cycle current at 100-μsec. intervals. (I) One hundred-second stimulus below cut. A slow, sustained rise was observed with return to normal seven minutes later. (II) One hundred ten-second stimulus above cut with no blood pressure effects. (III) One hundred thirty-five-second stimulus below cut and after extension of tractotomy on right side. Blood pressure rise was sustained for ten minutes with a slow return to control level after twenty minutes; (a) in I indicates a doubling of amplifier gain.

dad to the cut, with similar results (Fig. 3, I). However, when the cord was similarly stimulated a few millimeters cephalad to the cut, the blood pressure dropped from 100/68 to 80/55 mm. Hg (Fig. 3, II) and bradycardia occurred. This stimulation was repeated twice with comparable results (see table). At the end of the operation, the patient's blood pressure was 125/90 mm. Hg.

Case 3. M.B., a 75-year-old woman, underwent a chordotomy at C1 and C3 levels on the left side to control shoulder pain on May 9, 1958. The width of the spinal cord at C2 level was 12 mm., and the depth of the cut at the level of the dentate ligament was 5.5 mm. The blood pressure high in the left brachial artery was 260/130 mm. Hg following the tractotomies. With a 5-mm. bipolar

electrode at the level of the dentate ligament, the cord was stimulated with 90-cycle, 1.5-volt, 100-μsec. alternating current for ten seconds at 3 different cephalad levels. No change in peripheral arterial blood pressure was observed. When the same factors were used, stimulation a few millimeters caudad to the cut elevated the pressure from 250/150 to 280/170 mm. Hg. This effect lasted one minute, and then the pressure returned to the control level. A repeated stimulus elevated the pressure from 260/155 to 280/180 mm. Hg, which also lasted for one minute. During the third stimulation after replacement of the electrodes, marked irregularity of the heart beats and profound bradycardia (24 beats per minute) occurred and further stimulation was not carried out. At the end of the operation, the patient's blood pressure was 230/120 mm. Hg.

Case 4. M.C., a 56-year-old woman, underwent a cervical spinothalamic tractotomy at C2 level on the left side in May 1958. The width of the spinal cord was 11.5 mm. at this level. The entire anterior quadrant was divided for a depth of 5.5 mm. from the dentate ligament. Preoperative auscultatory blood pressure in the left arm was 124/90 mm. Hg. The right subclavian intraarterial blood pressure was recorded as 175/95 mm. Hg before the cut into the cord, in spite of partial heart block and dropped ventricular beats which produced a pulse rate of 56 beats per minute. Following tractotomy, the blood pressure stabilized at a level of 125/100 mm. Hg and the partial heart block lessened with a resulting pulse rate of 96. Stimulation with the bipolar electrode at 5-mm. depth cephalad to the cut, on a level with the dentate ligaments, produced no change in the blood pressure on 3 stimulations, each lasting five seconds, with 60-cycle, 3-volt, 100-μsec. alternating current. At the same depth caudad to the cut, stimulation with the above factors produced a rise to 140/115 mm. Hg on 3 occasions. Following the last stimulation, a marked increase in the heart block and dropped beats in the cardiac pulse were observed. Therefore, the procedure was terminated.

DISCUSSION

In these patients, elevation of the blood pressure was triggered between C1 and T2 along a straight line connecting the point of attachment of each dentate ligament to the spinal cord. Along this line, stimulation at depths of 1, 2, and 3 mm. did not produce a change in the blood pressure. At depths of 4 and 5 mm., depending on cord diameter, blood pressure responses were produced. In trying to determine the anatomic structure at these depths, one must consider the width of the spinal cord at the dentate ligament levels. Actually, the area of excitability in each cord was confined to an area of about 2 sq. mm.

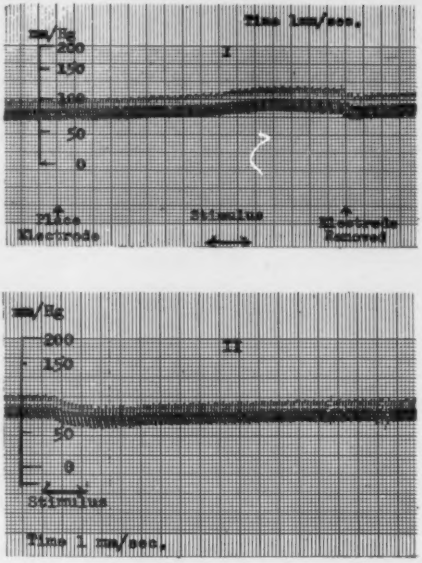

Fig. 3. Arterial blood pressure responses in Case 2 to spinal cord stimulation after tractotomy at T1 (left). Right T1 tractotomy was done three months earlier. (I) Arterial pressure rise was effected by ten seconds of 3-volt, 60-cycle, 100-μsec. biphasic alternating current below the cut in the cord. (II) Similar stimulation above the cut in the cord produced transient hypotension with bradycardia.

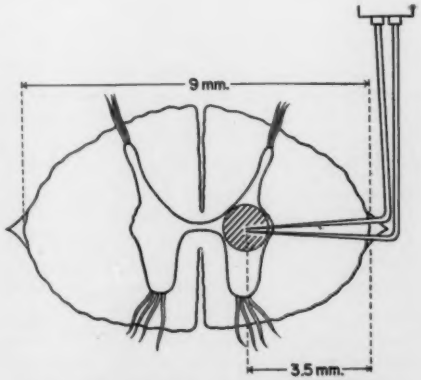

Fig. 4. Cross section of the human spinal cord at T1 level with bipolar electrode in the region of the cells of the intermediolateral column

This location roughly corresponds to the intermediolateral cell column (Fig. 4) but differs from the vasoconstrictor area described by Foerster[5] in man, and by Wang and Ranson[15] in cats. However, the generalized blood pressure elevation following unilateral stimulation of the cell bodies within the intermediolateral column on one side of the spinal cord remains unexplained. We cannot state that the cells of the intermediolateral column in the opposite half of the spinal cord were not activated by the same stimulus. As a matter of fact, the spread of the stimulus is highly possible.

These studies confirm clinical observations that the vasopressor mechanism within the upper spinal cord can be destroyed by radical tractotomy incisions. However, the destruction does not prevent adjustment of the peripheral blood pressure independent of the influence of the higher centers in the medulla and thalamus. The new level of blood pressure appears to be controlled by a reflex mechanism caudad to the level of the cut.

The bradycardia observed in Case 2 following central stimulation of the cut can be explained as a central reflex vagal mechanism. The slow rise of blood pressure suggests mediation of the vasopressor effect by the adrenal gland through the secretion of endogenous norepinephrine. The difference between arterial blood pressures measured by auscultation and by the intraarterial direct catheter method (see table) is partially explained by variations in the method but is primarily the result of gradient pressures downstream from the central pressure head. Auscultatory pressures were conventionally recorded from the antecubital space, while strain gauge pressures, always higher, were recorded from the catheter tip, which was placed more centrally in the subclavian artery. This fact, in addition to adrenal stimulation, may account for the failure of cord stimulation to elicit sharper blood pressure responses through peripheral arteriolar constriction. The more elastic major central arteries tend to dampen and thus mask a sharp arterial pressure rise observed more peripherally because of arteriolar constriction and decreased arterial to venous runoff.

SUMMARY

1. In 4 patients undergoing cervical or upper thoracic chordotomies, the cells of the intermediolateral column were stimulated. Caudad but not cephalad stimulation produced a slow rise in blood pressure.

2. In 3 patients who had not previously undergone bilateral spinothalamic tractotomy, the rise in blood pressure was of short duration (one or two minutes). In 1 patient who had undergone bilateral tractotomy two years earlier, the period of elevated blood pressure was longer (up to twenty minutes).

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Significance of pharmacologic state in recording optic potentials from cat cerebellum

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P. J. Harman, Ph.D., and C. A. Hovde, Ph.D.

EVOKED POTENTIAL methods were first applied to the visual areas of the cerebellum by Snider and Stowell[1] in 1942. Since then, Snider and associates[2–6] have contributed more data, as have Koella,[7,8] Whitlock[9] (in birds), and Bremer.[10] The distribution,[1–8] form,[8,20] sensitivity to drugs,[8] and interaction with other systems[1–6] have been clarified. During an extension of the work of Harman and Berry[11] to the distribution of photically induced potentials to the region caudal to the tentorium, it was noted that, unlike the striate cortex, which is responsive to photic stimulation even under deep barbiturate anesthesia, the cerebellum failed to generate significant spikes with or without barbiturates and, in fact, responded only when the animal was under the influence of drugs such as alpha-chloralose. Further, in consideration of the huge potentials found in the geniculate, superior colliculus, and striate cortex[11] and of the location of those structures relative to the different and ground leads usually employed in cerebellar recordings, it appeared that use of electrodes designed for sharp localization would be desired.

Although there are exceptions,[9,12,13] some of the best known investigations were done with chloralose and large monopolar electrodes. Perhaps more attention should be paid to the possible artifacts that might enter such experiments, as indicated by the above 2 factors. The use of chloralose and monopolar electrodes was justified in previous studies, because chloralose enhances the magnitude of evoked cerebellar potentials and large monopolar electrodes are appropriate for the study of wave forms. The present experiments were designed, however, to be carried out with reduced anesthesia and more localizing electrodes (bipolar), so that responses could be studied under conditions that might have more physiologic significance. Administration of chloralose for comparison and use of a variety of electrode arrangements were carried out. The findings from these experiments suggest that the importance, or at least the prominence, of photically evoked potentials in the cerebellum might need to be reevaluated.

MATERIALS AND METHODS

Operative procedure. The dura was exposed over the pyramis, tuber, and the area more rostral, up to the primary fissure. This cortex included all of lobules VI, VII, and VIII of Larsell[14] and much of the visually active area previously described.[3,8] In many animals, an area was also exposed over the striate cortex, so that cerebellar and cerebral potentials could be recorded simultaneously. The cat was then oriented in a stereotaxic apparatus. The above procedure was carried out with light ether anesthesia delivered with artificial respiration through a tracheal cannula. In a few cats, local Xylocaine was substituted for the ether. When necessary, 2 to 4 mg. doses of Flaxedil were given by polyethylene venous catheter inserted into the femoral vein. After one hour or longer following cessation of ether, the

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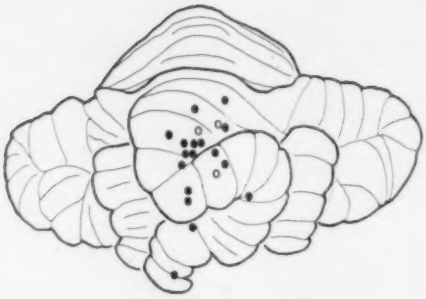

Fig. 1. A semischematic diagram of the posterior cerebellar cortex of the cat, showing the distribution of points from which recordings (1 animal per point) were taken by combinations of monopolar and bipolar electrodes. O represents points that showed no response throughout the entire experiment; the cat was immobilized with Flaxedil, and no other anesthetic agent was employed. • represents points which showed no response before alpha-chloralose and an active response after the intravenous administration of 50 mg. per kilogram of alpha-chloralose.

dura was carefully removed over the areas to be studied and electrodes placed on surface and in depth in an attempt to explore and map all active areas in the cerebellum. Many of the more critical experiments designed to study anesthetic effects were carried out with minimum movement of the electrodes on the surface.

Electrodes. Two types of electrodes were constructed for use in a variety of arrangements. Single small needles, either 00 insect pins or No. 18 beading needles, were joined to a shaft of syringe needle tubing and insulated with clear baking enamel. The electrode was ground to expose a 40 to 75 μ tip. For bipolar electrodes, 2 of the needles were cemented together with baking enamel, with the tips placed 50 to 100 μ apart.

Since the arrangement of the electrodes in 2- or 3-needle carriers of the stereotaxic device was critical to each type of experiment, description of the electrode placement will be included under "Results" below. After passing through cathode-loaded input stages, the action potentials were amplified through Grass P6 preamplifier, delivered to a DuMont 322-A dual beam oscilloscope, and photographed with a Grass camera. The amplifiers were adjusted to allow a high degree of differential action (common signal rejection).

Stimulation. Photic stimulation was delivered by a Grass Model PS-2, which was triggered at a controllable point on the sweep by a Grass S-4 stimulator. The parabolic lamp and reflector were placed 10 to 12 in. from the cornea. With this arrangement, the manufacturer's specifications indicate that about 7.5×10^5 or 3.7×10^5 candle power of light, depending on the intensity setting of the Grass PS-2, was projected to a circular area of the retina extending nasally and ventrally from the macula. The area illuminated would be determined from the 15° arc of the cone of light to the eye. The duration of the flash was approximately 10 μsec. Therefore, the stimulus was extremely brief and intense. An intense stimulus was used in preference to a weak one, in order to drive the optic pathways after it was found that little, if any, response was obtained in the unanesthetized animal under the conditions of the experiments.

Types of experiments. The experimental procedures used on the 56 cats employed may be classified into 2 groups. In both groups, however, the basic condition was the use of ether or local Xylocaine for preliminary surgery, followed by an interval of more than an hour, with Flaxedil after cessation of ether before recording began. In a few cases, d-tubocurarine was used instead of Flaxedil.

In the first group of experiments, recording of cerebellar potentials was carried out with both bipolar and unipolar electrodes. Photic stimulation was alternated with sciatic nerve stimulation before and after the administration of 50 mg. per kilogram of alpha-chloralose. The sciatic stimulation was used as a control procedure to verify the reactivity of the cerebellum.

In the second group, instead of using 2 points of stimulation, 2 points were recorded from simultaneously. In this way, the effectiveness of the photic stimuli could be recorded at the striate cortex; thus, the functioning of the stimulator, retina, and portions of the optic pathways were controlled. The simultaneous record from the cerebellum could also be compared directly to the cerebral response.

As a terminal procedure, other drug agents were employed after comparison of evoked potentials recorded before and after alpha-chloralose. For instance, in a few experiments, small amounts of Nembutal (12 mg.) were added through the venous cannula at short intervals (e.g., ten seconds) and records were taken every ten seconds over a period of several minutes (Fig. 6).

RESULTS

Failure to obtain photically evoked potentials without drugs. The extent of exploration of the surface of the cerebellum is diagrammed in Figure 1. The points recorded from represent a compilation of points from 26 cats, which were chosen because recordings were taken at only one point in the entire experiment. In other cats, a more systematic search was made, with many points of recording in a single experiment. These were not included in the diagram, even though no significant spikes appeared before alpha-chloralose, in order not to magnify the negative data. Therefore, the diagram shows points which all produced no large evoked potentials before an excitant drug was given and represents one relatively negative finding per point under conditions described below. The terms "relatively negative" and "or very small" refer to questionable and very small potentials that may represent field effects, were rarely present, and were disclosed only when monopolar electrodes were used, as in Figures 4*a* and *b*.

The conditions under which

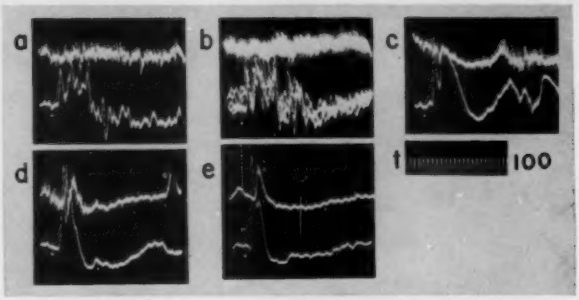

Fig. 2. In 350-msec. sweeps, simultaneous bipolar recordings from the cerebellar cortex (top trace) and the striate cortex (bottom trace) of cat 54. Cat was immobilized with Flaxedil and other drugs as indicated. [a] Shows no response in the cerebellum and complex response in the striate cortex before administration of alpha-chloralose. [b] Superimposition of 5 consecutive sweeps, as in *a*, separated by ten seconds between successive sweeps. Note that, while the striate response is obvious and definite, the cerebellar response without chloralose is either absent or very small. [c] two minutes; [d] thirteen minutes; and [e] seventy-eight minutes following intravenous administration of 50 mg. per kilogram of alpha-chloralose show the progressive development of the cerebellar response to photic stimuli with time. Note the gradual depression of background activity and the correspondence of the cerebellar wave with the second wave of the striate response.

Upward deflection is negative. Time line = 100 cycles per second (10 msec. peak to peak).

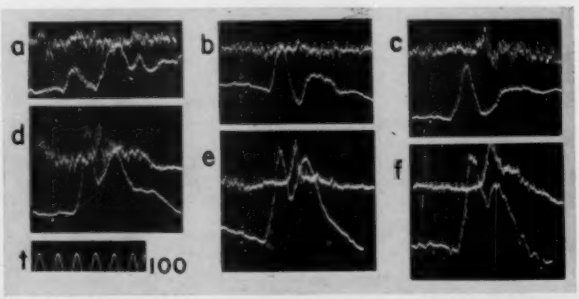

Fig. 3. In 70-msec. sweeps, a series of simultaneous bipolar recordings taken from the same point as those shown in Figure 2, cerebellar trace on top and striate cortex on the bottom, showing progressive development in the amplitude and form of the cerebellar response to photic stimuli under the influence of alpha-chloralose. [a] no chloralose; [b] one minute; [c] one and one-half minutes; [d] eighteen minutes; [e] twenty-eight minutes; and [f] seventy minutes after the intravenous administration of alphachloralose, 50 mg. per kilogram. Note apparent absence of response in trace *a* and its gradual appearance in traces *b* through *f*. Also note the increase in random spiking following the main response and the late "depression" of this spiking which follows (traces *c* and *d*). In *e* and *f*, the correspondence of the arrival of the cerebellar response with the beginning of the second portion of the striate response can be seen.

Upward deflection is negative. Time line = 100 cycles per second (10 msec. peak to peak).

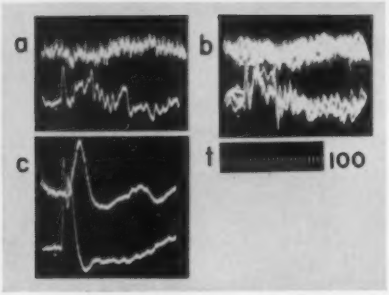

Fig. 4. In 350-msec. sweeps, simultaneous recordings taken from a single point of the cerebellar cortex (monopolar—top trace) and the striate cortex (bipolar—bottom trace) of cat 54, showing the response to photic stimuli. The indifferent electrode used with the cerebellar recording was placed on the bone of the midsagittal suture, about midway in its anteroposterior length. [a] The response patterns obtained before administration of alpha-chloralose. Note apparent absence of cerebellar response. [b] Superimposition of 5 consecutive sweeps separated by ten seconds between successive sweeps before administration of alpha-chloralose. [c] Forty minutes after intravenous administration of 50 mg. per kilogram of alpha-chloralose, showing full blown cerebellar response to photic stimulus and the correspondence with second wave of the striate response. Compare amplitude and duration of cerebellar response with Figure 2*e* (bipolar recording).

Upward deflection is negative. Time line = 100 cycles per second (10 msec. peak to peak).

no or very small spikes were obtained were variable when recordings were made from points in Figure 1. In 10 animals, the electrode placement was monopolar on the cerebellum with a second electrode of similar construction placed in a presumably inactive area such as the diploë, either lateral or caudal to the different electrode. The indifferent electrode was not grounded, but, instead, the ground was placed separately on the metal of the stereotaxic instrument or on neck muscles. Thus, the advantages of differential recording, such as elimination of aerial effects and cardiac potential fields, were applied to an essentially unipolar arrangement. In 20 other animals, bipolar electrodes with tips 50 to 100 μ apart were placed on the cerebellum at 20 of the points on Figure 1. These 20 points, however, also represent points of monopolar recording, since 1 of the electrodes was switched off, leaving the other electrode of the pair as the different electrode. The switch was thrown to another electrode duplicating the monopolar arrangement described above. A third arrangement contained a single electrode as a different electrode on the cerebellum, an indifferent single electrode that could be moved to various inactive positions, and a separate ground. This arrangement is essentially monopolar. Such an arrangement, which could be switched, was used in Figures 2 through 5 to produce both unipolar and bipolar records.

No evoked potentials were found under the varied electrode arrangements in the absence of alpha-chloralose.

At nearly every point, either the viability of the cerebellum was tested by sciatic stimulation or the functional integrity of the optic system was demonstrated by recording from the striate cortex.

A series of records from 1 animal (No. 54), in which no cerebellar response to photic stimulation was seen under the above conditions, appears in Figures 2 through 5. Figures 2*a* and *b* and Figure 3*a* show no evoked potential with bipolar electrodes and at different sweep speeds before alpha-chloralose was given. All of these records were taken from an electrode arrangement placed in the caudalmost part of VII A^{14} of the tuber. Figure 2*b* is more important or more critical, since the upper sweep of that record shows no identifiable cerebellar potential after optic stimulation in 5 successive sweeps. Furthermore, the sweep is slow, which tends to clarify small deviations by the increase in slope. The records in Figures 4 and 5 were from the same cat as in Figures 2 and 3 and were made in the order of 2*a*, 2*b*, 3*a*, 4*a*, 4*b*, 5*a*. Before chloralose, the monopolar recording in Figure 4*a* shows a slow (long) negative deviation of low amplitude (about 60 μv.). In repeated frames, not illustrated, the wave often was not present. In 4*b*, the more critical multiple sweep (5 sweeps), the slow wave is less obvious. In Figure 5*a* with a more rapid sweep,

no spike appears in the earlier part of the record, where spikes will appear under chloralose, as in the upper trace of 5*c*. Note that potentials from the striate cortex responded in all instances.

Thus, no unequivocal photically evoked potentials were found under the above conditions of electrodes and reduced drug influence.

Development and characteristics of potentials with alpha-chloralose. The description of potentials following alpha-chloralose will be brief, because more emphasis will be placed on features not emphasized in previous work. In the typical experiment of cat 54, (Figs. 2–5), 50 mg. per kilogram of alpha-chloralose was injected quickly into the femoral vein through polyethylene tubing. Although several minutes were required for evoked potentials to increase to a maximum, significant changes appeared promptly after chloralose injection. In Figure 3*b*, one minute after chloralose, a short and very small negative burst appeared at the cerebellum (upper trace) with a 27-msec. latency, followed by a random increase in activity lasting about 20 msec. The spike and increased activity of about 40-msec. duration appears clearly in Figure 3*c*, one and one-half minutes after injection of alpha-chloralose.

A significant decrease in activity, reminiscent of inhibition or a silent period, appears later on the sweep (Fig. 3*d*). This inhibition might be considered with the well-known rebound phenomenon of the cerebellum. Shifting to the slower sweep, in Figure 2*c* taken two minutes after chloralose, the "inhibition" after the burst and increased activity began about 50 msec. after the photic stimulus. The depressed part of the spike lasted for more than 100 msec. This consistent finding of depressed activity is also found in all of the slow sweep records and persists until the entire background activity is depressed, either by exposure and deterioration of cerebellar cortex or by prolonged influence of the drug. Thus, in the bipolar records Figure 2*d* at thirteen minutes after chloralose and 4*c* at forty minutes, the "inhibition" is clear. Typically, at longer intervals following chloralose, the whole background activity of the cerebellar cortex subsides, as in Figure 2*e* at seventy-eight minutes after alpha-chloralose.

The general wave form of the large negative

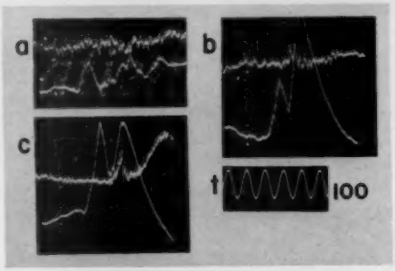

Fig. 5. In 70-msec. sweeps, simultaneous monopolar cerebellar cortical recordings (top trace), and bipolar striate cortex recordings (bottom trace) in cat 54. [a] Before administration of alpha-chloralose; animal immobilized with Flaxedil. [b] Thirty-six minutes after administration of 50 mg. per kilogram alpha-chloralose. [c] Seventy-two minutes after administration of alpha-chloralose. Note "depression" of spontaneous background activity with time and the increase in amplitude of the cerebellar and striate waves.

Upward deflection is negative. Time line = 100 cycles per second (10 msec. peak to peak).

cerebellar potential under chloralose was similar to that described by Koella[8] and Snider[3] using monopolar electrodes. The magnitude was 210 μv. with a monopolar electrode in Figure 3*c* (upper trace) and reached more than 300 μv. in other animals. The latency in Figures 3 and 5 (bipolar and monopolar) was 22 to 27 msec. and seldom attained 40 msec. in other cats. This brief latency (compared to Koella's 22 to 90 msec.) is consistent with the intense stimulus employed in our study. Additional excitants such as picrotoxin received some secondary attention. When picrotoxin was added at the end of an experiment, the cerebellar spike increased to nearly double the magnitude under alpha-chloralose alone.

Comparison of cerebellar and striate area potentials. The beginning of the evoked photic potential of the cerebellum under chloralose (top traces, Figs. 2–6) possessed a longer latency or conduction time than those of the striate cortex of the cerebrum. By an interesting coincidence, the large cerebellar negative potential begins at the time at which the second large deviation is seen with bipolar

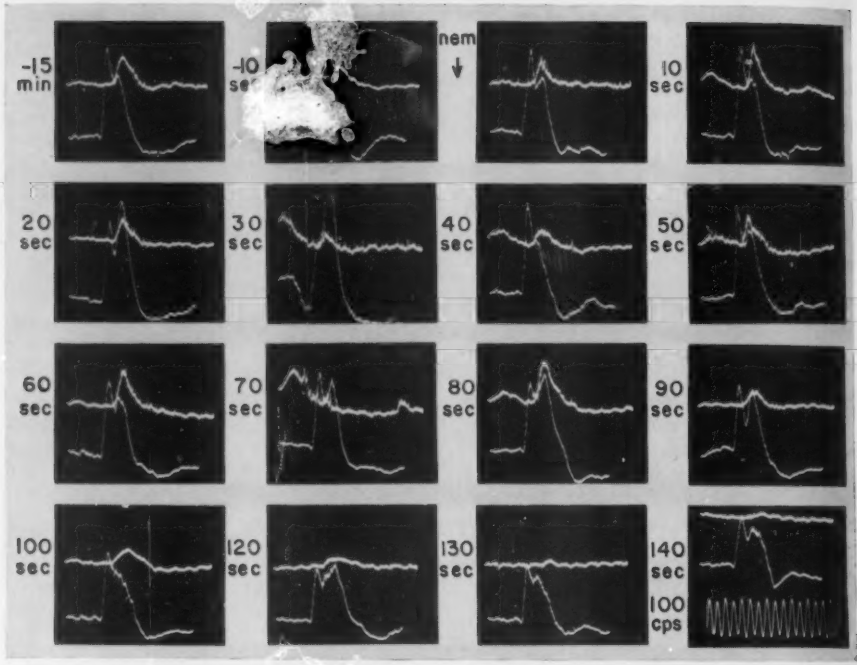

Fig. 6. A series of simultaneous bipolar recordings taken from the cerebellar cortex (lobule VII —top trace) and striate cortex, showing the depressant effects of Nembutal upon the cerebellar and cerebral responses to photic stimuli. In a cat immobilized with Flaxedil and narcotized by intravenous injection of 50 mg. per kilogram of alpha-chloralose, typical cerebellar responses were obtained as in traces labeled –15 min. and –10 sec. At this point, 5 mg. per kilogram of Nembutal was injected intravenously at ten second intervals immediately after the recording. The cerebellar response is almost completely abolished, as shown at 130 and 140 sec. traces. The striate response, although affected, is merely reduced in amplitude. Apparent enhancement of the cerebellar response occurs at 50, 60, and 80 msec., while enhancement of the striate response occurs at 20 and 30 msec., indicating perhaps a differential susceptibility. Upward deflection is negative. Time line = 100 cycles per second (10 msec. peak to peak).

electrodes on the cerebrum. The latency of 11 to 13 msec. to the first striate potential and 22 to 27 msec. to the cerebellar potential (Figs. 2–5) is extremely brief. Since the retinal delay, which is a major factor in this delay, varies inversely with light intensity and duration,[8] the extremely intense light used explains the brevity of the latency.

Action of Nembutal on evoked potentials. The events following the administration of Nembutal by femoral catheter to an animal already under the influence of chloralose revealed 2 features. First, the resultant depression of photically evoked potentials did not occur immediately; these responses may be enhanced slightly during part of the first minute after injection. Second, the cerebellar photic potentials are more quickly and completely depressed than striate photic potentials.

The above 2 features were demonstrated more easily when multiple small doses of Nembutal were injected at brief intervals and records also taken at brief intervals. Thus, in Figure 6, 5 mg. per kilogram of Nembutal was injected every ten seconds just before a record was made. The cerebellar potentials waxed and waned, as they also did in Figures 2 through 5, but rather large spikes at fifty, sixty,

and eighty seconds show that the evoked cerebellar potentials do not disappear immediately and may be enhanced before disappearing.

The influence of Nembutal on the simultaneously recorded striate cortex potential is also shown in Figure 6. The spikes recorded soon after the Nembutal injections were started are not depressed. The records at twenty and thirty seconds are larger than the 2 controls at fifteen minutes and at ten seconds prior to Nembutal injection. Durability of the cerebral cortical potential compared to cerebellar potential is also seen in Figure 6, in which magnitude of the striate potential is still more than half the control level when the cerebellar potential is almost nonexistent.

DISCUSSION

Apparently, there is a great difference between cerebellar potentials evoked by photic stimuli and those evoked through somatic afferent systems. In the present experiments, no significant spikes, waves, or suppression of spontaneous activity occurred under conditions approaching the unanesthetized state following photic stimulation. With chloralose, however, striking evoked potentials appeared, as previously reported by many workers.[1-4,8,15] Exceptions to the above statements can be found in the work of Whitlock,[9] who found optic cerebellar potentials in essentially unanesthetized birds, and in the work of Buser and Rouguel,[12] who also found optic cerebellar potentials in pigeons after electrical stimulation of the optic nerve utilizing only local anesthetics at the site of surgical intervention. Fadiga, Pupilli, and von Berger[13] found surface optic cerebellar potentials in cats immobilized with curare-like compounds, both before and after administration of chloralose. These last authors remarked on the fact that the use of chloralose produced a more widespread activation of the cerebellar cortex than could be seen before its administration and that the characteristics of latency and wave form underwent definite change. That much of the knowledge and interpretation of cerebellar visual areas has been gathered from chloralose-treated animals may have led to a misconception concerning the functional importance of the visual projection to the cerebellum. It might even be suggested that the visual-cerebellar system may not normally function, although this statement has been disputed by Fadiga and associates.[13]

Somatic afferent projections, by contrast with the visual, seem to evoke cerebellar potentials with ease, without the special condition of the use of chloralose[9,10,16,17] and, in many reports, in the presence of Nembutal.[18,19] Combs[18] actually found better localizations of spinocerebellar areas with Nembutal.

Frequency of stimulation, waxing-waning of potentials (chloralose), and suppression of the evoked potentials by measured doses of barbiturate—3 features of photic potentials of the cerebellum—were carefully described by Koella[8] and are completely confirmed here. Throughout all the present experiments, the variability of potential magnitude was not only observed but was troublesome. A specific example of possible misinterpretation of the influence of Nembutal occurs in Figure 6. Here increase of potential magnitude very soon after injection of Nembutal might be an example of cerebellar potential variability.

The general features of the wave form obtained under the influence of alpha-chloralose were similar to those seen by Snider[3] and Koella.[8] Perhaps the direction of the first large wave was more consistently in a negative direction. Koella[8] described the direction as variable in his experiments, and, in his Figure 4, they were negative (see also Morin and associates[20] and Fadiga and associates[13]). Latency, with intensity considered, and magnitude of the waves were similar. A major difference in our records is the absence of the first potential, which Koella emphasized and which was also seen and described by Fadiga and associates[13] in both unanesthetized and chloralose-treated cats. That it was not seen in the present experiments with either bipolar or with the rather special form of monopolar electrode is significant, since the later waves were observed by us in cats under chloralose. The difference in the electrodes may be important. The special arrangement of the monopolar electrode with matched and differentially amplified different and indifferent pickups provides an opportunity to study both local activity and "monopolar" generalized activity. Since the present electrodes were small, either the firing of local units masked this early

negative wave or the better localization of small electrodes did not record the spreading potential of an incoming volley while it was at a distance. Such a pickup of local activity reached a high level, including "spikes" from single units, in the study of spontaneous cerebellar activity by Brookhart, Moruzzi, and Snider,[16] but they did not observe any change in slower "waves" when they compared the records from a microelectrode and a large monopolar electrode.

The finding of either inhibition or at least a decrease in the spontaneous activity of the cerebellum associated with the appearance of a photically evoked potential may have functional significance. (Inhibition may be a somewhat misleading term when applied to the cerebellum; Purpura and Grundfest[21] have suggested that there is an absence or deficiency of inhibitory synapses in the cerebellum.) Brookhart, Moruzzi, and Snider[17] observed a decrease in activity of single units upon the arrival of afferent impulses from a limb and pointed out the relationship of such depression of spontaneous activity to the well-known phenomenon of cerebellar rebound. The present results, which show waves, depression, and recovery, might be correlated with the first 2 stages of the long term alternation of complex movements following stimulation of implanted electrodes.[22]

The observation of longer latencies of cerebellar potentials compared to simultaneously recorded potentials evoked in the striate cortex may prove important in interpretation of the possible course of visual pathways to the cerebellum. It might be emphasized here that the method of simultaneous recording from more than one optically active area following photic stimulation of the retina has the advantage that, under these conditions, variations related to retinal delay and electrical responsiveness of the central nervous system in different animals are eliminated. Although some work has been done on the identification of visual pathways to the cerebellum,[2] optic impulses have not been traced in a systemic way from retina to cerebellum nor have recording arrangements designed for a high degree of localization of signals been applied to this problem. Extension of the method of simultaneous differential recording with small bipolar electrodes, as utilized in this study, might clarify some of the discrepancies between our results and those of others. Further, such investigations could be designed to eliminate any possibility that visual potentials in the cerebellum represent artifactual electrical spread from neighboring optically active areas.

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Electrical wave forms recorded from the cerebellar hemispheres

Alma M. Stoiber, Ph.D.

EVOKED POTENTIALS as recorded from the cerebellar hemispheres after stimulation of the cerebral cortex have been described by Curtis,[2] Dow,[3,4] Hampson,[7] Jansen,[8] and Fadiga, Pupilli, and von Berger.[5,6] A great variety of wave forms and polarity of such potentials exist in the reported results. The present paper attempts to explain that such variations are related to the exact cerebellar point from which the recording was made. Consistent potentials can be recorded if the pickup point remains the same, providing other experimental conditions are unchanged.

MATERIALS AND METHODS

The experiments were carried out using adult cats anesthetized with intraperitoneal injections of 15 mg. each of Nembutal and chloralose per kilogram of body weight. Small supplementary doses of each anesthetic agent were administered as needed while the experiment proceeded, care being taken to keep the ratio of the amounts of drugs the same as originally given. The anesthetic level was never so deep that pressure on the toe pad failed to elicit a brisk flexor response.

Bone was removed so as to expose cerebral cortex on the right and cerebellum on the left. In the case of the latter, the superior surface of the cerebellar hemisphere was uncovered, along with a portion of the anterior lobe and the vermis. After the dura was reflected, the brain surfaces were irrigated with warm mineral oil. When drugs were locally applied, small squares of filter paper soaked with the appropriate solution were used, application being directly to the surface without the use of mineral oil.

The stimulation electrodes were bipolar silver wires embedded in glass, except for the tips, with an interpolar distance of 2 mm. The recording electrodes were saline-soaked, cotton wick, silver ball type. When monopolar recordings were done, a silver plate was buried within the neck muscles to serve as the reference point. Surface negative signals were recorded in an upward direction.

Shocks generated by a Grass stimulator (model 3C) were delivered through a Grass isolation unit at a rate of once every two seconds. The shocks were biphasic, 0.5 msec. in duration, and from 8 to 15 volts in strength. The evoked potentials were amplified by a Grass preamplifier (model P4), visualized on a Hewlett-Packard single beam oscilloscope, and photographed. Fast spontaneous cerebellar activity was filtered out electronically. Latencies were measured from the beginning of the shock artifact to the peak of the response.

RESULTS

With pickup electrodes placed transverse to the main axis of the cerebellum, about 7 mm. apart upon crus I or II, recordings were made after stimulation of various areas of the contralateral cerebral cortex. A response was more readily obtained after stimulation of the anterior sigmoid gyrus than with any other cerebral area. A suprathreshold (8 volts) shock for the anterior sigmoid gyrus was subthreshold for other cerebral areas. A stronger shock (12 volts) was suprathreshold for all cortical areas and would elicit a cerebellar response of higher amplitude from the anterior sigmoid gyrus than from any other cortical area. In most cases, suprathreshold (12 volts) stimulation of the anterior sigmoid gyrus

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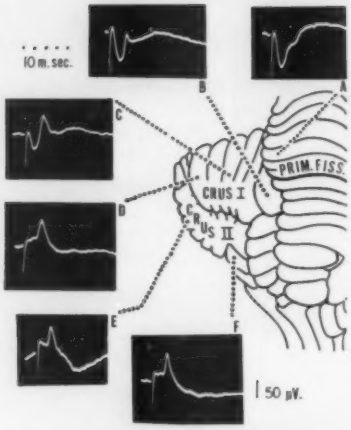

Fig. 1. Monopolar recordings taken from 6 points on the cerebellar cortex after stimulation of the contralateral anterior sigmoid gyrus. [A] Record from the anterior lobe. [B] Record from the most medial folium of crus I. [C] Record from an intermediate position on crus I. [D] Record from a lateral folium of crus I. [E] Record from a lateral folium of crus II. [F] Record from a medial folium of crus II

elicited a sizable response, and stimulation of the posterior sigmoid gyrus evoked a response of lesser amplitude. If the same shock was then given to the anterior extent of the lateral, the midsuprasylvian, coronal, middle ectosylvian, and sylvian gyri, still smaller response resulted. Shocks applied to the posterior suprasylvian, posterior ectosylvian, and posterior portion of the middle suprasylvian gyri failed to initiate evoked responses in crus I and II, even when high voltages (up to 40 volts) were utilized. In general, cerebellar responses followed stimulation of those areas designated as excitable motor cortex in the cat, as published by Murphy and Gellhorn.[10]

The thresholds of the observed responses were elevated by extra amounts of anesthetic agent. If, for example, additional Nembutal had to be used in order to induce anesthesia initially, stimulation of only the anterior sigmoid gyrus would elicit a cerebellar response. This response was reduced or absent, particularly from the more lateral aspect of the hemisphere. This depressant effect of Nembutal can explain the differences between the responses reported in this paper and those reported by Snider and Eldred,[11] since those authors gave their animals considerably more Nembutal than was utilized in the present study.

The wave forms as recorded monopolarly are illustrated in Figure 1. The tracing from the anterior lobe in Figure IA shows a surface-positive deflection with a latency of 9 msec., followed by a prolonged negative potential of low magnitude. A record taken from the medial aspect of crus I (Fig. 1B) also shows a prominent surface-positive deflection, while that taken from an intermediate position (Fig. 1C) shows a positive deflection followed by a distinct negative potential. A prominent surface-negative potential is recorded from the

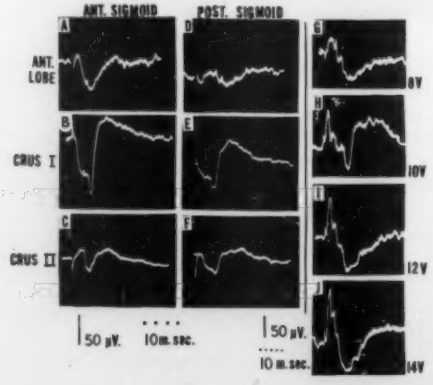

Fig. 2. Bipolar recordings taken from 3 cerebellar areas after stimulation of either the anterior or posterior sigmoid gyrus of the contralateral cerebral cortex. Cat under Nembutal and chloralose anesthesia. Records after threshold stimulation of the contralateral anterior sigmoid gyrus: [A] Record from the anterior lobe. [B] Record from crus I. [C] Record from crus II. Records obtained after threshold stimulation of the contralateral posterior sigmoid gyrus: [D] Record from the anterior lobe. [E] Record from crus I. [F] Record from crus II. [G through J] Records taken from crus I after stimulation of the contralateral anterior sigmoid gyrus, using a gradually increasing stimulating voltage. Voltages noted at right of each frame. Polarity of recording electrodes reversed as compared with A, B, and C

lateral part of crus I (Fig. 1D) and from 2 locations on crus II (Fig. 1E and F). Thus, under these experimental conditions, certain areas of the cerebellum present positive potentials while others show negative ones.

Typical responses as recorded with bipolar electrodes are illustrated in Figure 2. Stimulation of the anterior sigmoid gyrus produced a response in the contralateral anterior lobe, whereas stimulation of the posterior sigmoid gyrus did not, if the same recording site and the same stimulating voltage were used in each case. The response recorded from crus I (Fig. 2B) subsequent to anterior sigmoid gyrus stimulation is characterized by 2 unidirectional peaks followed by an after potential in the opposite direction. The latency to the first peak is from 8 to 16 msec. and to the second peak, from 14 to 28 msec. Responses observed in crus II are of lower amplitude than those in crus I, providing the stimulating voltage is kept constant. The wave form of bipolar recordings taken from crus I varies with increasing strength of stimulating voltage applied to the cerebral cortex, as illustrated in Figure 2C through J. An initial peak develops, which increases gradually in height but does not change in latency.

With bipolar recording from crus I after stimulation of the contralateral anterior sigmoid gyrus (1 electrode on the most medial folium, the other on the most lateral), the response illustrated in Figure 3A results. When this is compared with responses recorded monopolarly (Fig. 3B and C), it can be seen that the initial positivity taken from the medial electrode coincides with the first peak of the bipolar record. The second peak of the bipolar record coincides with latency of the peak of the negative potential recorded monopolarly from the lateral position (Fig. 3C). Thus, a potential recorded by means of bipolar electrodes, if oriented mediolaterally on crus I, will show a short latency peak indicative of positivity near the medial electrode and a longer latency peak of induced negativity near the lateral electrode.

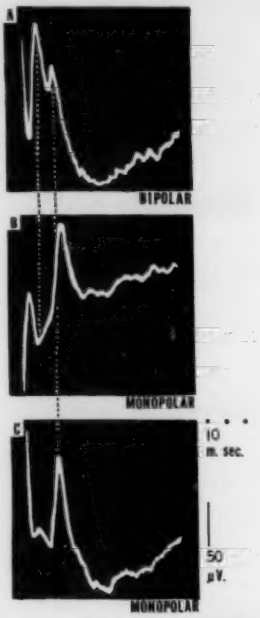

Fig. 3. Bipolar and monopolar records obtained from crus I after stimulation of the contralateral anterior sigmoid gyrus. [A] Bipolar record—1 electrode on the most medial folium, the other on the most lateral folium. [B] Monopolar record from the medial folium. [C] Monopolar record from the lateral folium

A question could be asked as to the source of these responses. It might be considered, for example, that the positive response indicates conduction along a pathway of fibers beneath the surface and the negative component could then be the result of cellular activity within the neuronal aggregate that comprises the cerebellar cortex. Since cellular activity is more easily depressed than fiber activity by drugs and asphyxia, this technic was used as a means of collecting additional data on the source of these potentials. Observations were made using suprathreshold stimulation of the anterior sigmoid gyrus with recordings that were taken from contralateral crus I.

Data shown in Figure 4A through C indicate that the second peak of the usual bipolar record can easily be reduced by the use of topically applied Nembutal solution. A small square of filter paper soaked in this solution was placed on the cortex at the point at which the lateral electrode made contact, allowed to remain for two minutes, and then removed.

The bipolar record demonstrated a reduction of the second peak as seen in Figure 4B after liberal irrigation of the cerebellar cortex with warm physiologic saline solution, the usual response [C] was observed after excitation of the sigmoid gyrus.

The effects of topically applied procaine are shown in Figure 4D through G. A control trace was taken; then small squares of filter

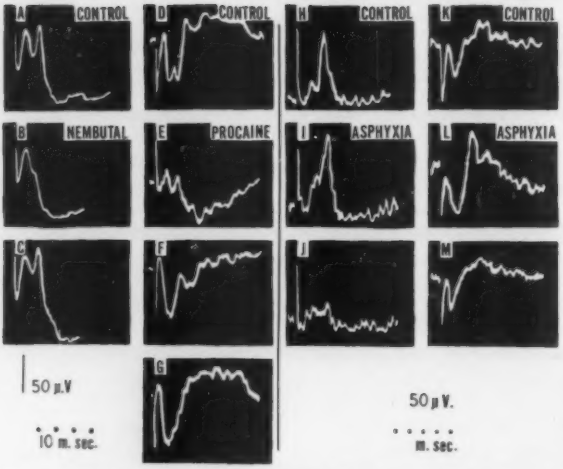

Fig. 4. Bipolar and monopolar records from crus I after stimulation of the contralateral anterior sigmoid gyrus, showing the effects of topically applied procaine and Nembutal and of general asphyxia. Effect of Nembutal: [A] Control record with electrodes placed transversely across crus I. [B] Bipolar record taken after application of Nembutal solution beneath the lateral electrode. [C] Bipolar record as in A and B. Reversal of effect of procaine. [D] Bipolar control record. [E] Monopolar record from lateral folium of crus I after procaine. [F] Monopolar record from medial folium of crus I after procaine. [G] Bipolar record as in D after procaine. Effect of asphyxia: [H] Monopolar control record from lateral folium of crus I. [I] Monopolar record as in H after occlusion of tracheal cannula for one minute. [J] Monopolar recording as in H after occlusion of tracheal cannula for one and one-half minutes. [K] Monopolar record from medial folium of crus I. [L] Monopolar record as in K after occlusion of tracheal cannula for one minute. [M] Monopolar recording as in K after occlusion of tracheal cannula for one and one-half minutes

paper soaked in 2% procaine solution were applied briefly to the 2 points occupied by the electrodes. Recordings were repeated as follows: in Figure 4E is shown a monopolar record taken from the lateral part of crus I; note that there is very little activity. In Figure 4F is shown a record taken from the medial aspect of crus I, which reflects the usual surface-positive, short latency response. The bipolar record that follows in Figure 4G reveals only the shorter-latency peak.

In Figure 4H is illustrated a control response recorded monopolarly from the lateral part of crus I, which reveals the usual surface negative activity. After one-minute occlusion of the tracheal cannula, the tracing shown in Figure 4I was obtained. After one and one-half minutes of tracheal occlusion, this surface-negative response is reduced to that shown in Figure 4J. Figure 4K is a monopolar tracing taken from the medial aspect of crus I for control purposes. The photograph in Figure 4L shows a trace taken one minute after tracheal occlusion, and that in Figure 4M, one and one-half minutes after the same maneuver. Note that the surface-positive response persists. Thus, it has been shown that the surface-negative wave is more readily depressed by topically applied Nembutal and is more sensitive to procaine and asphyxia than is the surface-positive wave. These observations support the concept that the positive wave represents deep fiber activity, while the negative wave represents activity in the more superficially located cell bodies. The surface-negative response is more variable in appearance than is the positive response, and, if the condition of the animal were poor, the surface-positive potential was usually present, while the surface-negative potential was not.

DISCUSSION

The present work is concerned primarily with cerebellar responses recorded from crura I and II following stimulation of the contralateral cerebral cortex. Excellent studies on vermian and paravermian lobule responses are to be found in the papers of Dow,[3,4] Jansen,[8] Morin, Catalano, and Larmarche,[9] and Snider and Eldred.[11]

The contour and polarity of the evoked cerebellar potential as recorded from the hemispheres have been variously described by a number of investigators. Dow[3,4] reported a surface-positive potential followed by a longer lasting, surface-negative potential accompany-

ing stimulation of the pons. The potentials resembled the present ones taken from the more medial aspects of crus I. Also, Dow reported a surface-positive response that changed in an unpredictable manner when the recording electrode was moved a short distance.

The recent extensive paper by Jansen[8] contains detailed descriptions of cerebellar recordings made after cerebral stimulation. Jansen reported that potentials recorded from crus I were often surface-negative and of both short and long latencies. The long latency potentials occur within the time range of the presently reported surface-negative recordings and correspond to the second peak of the potentials recorded from crus I. The short latency potentials are also within the range of surface-positive waves reported herein and probably correspond to the first peak in the bipolar record. Jansen also reported one instance of a reversal in polarity of the cerebellar potential after a change in the cerebral area stimulated, with the recording point remaining the same. This was never observed in the present experiments. The polarity of the response remains unchanged regardless of the area stimulated and is consistent in relation to the recording site. Jansen attributes the short latency potential to activity within the granular cell layer and the long latency one to the Purkinje cells. The later surface-negative wave is associated with the activity of Purkinje cell dendrites. The present report is not concerned with a detailed analysis of the source of these potentials.

Morin, Catalano, and Lamarche[9] have also done a careful study of the wave forms in the paramedian lobule. They describe, with monopolar recording, an initial positive deflection termed "x," followed by a biphasic wave termed "y." The "x" deflection is interpreted as due to the activation of the granular layer and the "y" potentials, to Purkinje cell activity. Thus, there is general agreement with Jansen.

Potentials, as recorded by Snider and Stowell[12] from the tactile receiving areas of the cerebellum, were surface-positive, often preceded by a small wave of negativity. Sometimes, they report, the responses were triphasic with negative, positive, and negative components, in that order. Snider and Eldred[11] observed potentials in the contralateral culmen, with some overlapping into crura I and II after stimulation of the cerebral motor (arm) area. The usual response was a surface-positive wave, sometimes preceded and/or followed by a negative wave. Thus, their observations would be compatible with the present findings.

Bremer and Bonnet[1] analyzed cerebellar recordings and concluded that the initial positive deflection represented afferent influx and activity along axons of interneurons that relay the influx. The negative spike represented, in their opinion, synchronous discharge by the Purkinje cells, and the surface-negative wave was due to cerebellar afferents firing asynchronously.

Fadiga, Pupilli, and von Berger[5,6] have presented a summary of surface cerebellar potentials as recorded monopolarly under chloralose anesthesia after visual stimuli. Records taken from the vermis show a surface-positive deflection followed by a smaller surface-negative one. Recordings from the crura yielded predominantly negative potentials. They concluded that the initial positivity of the responses led from the vermis and from crus I as well, since the positive inflection superimposed on the surface-negative response of crus I might be partly due to postsynaptic activation of granular cells and also to presynaptic activity in the afferent fibers. Repetitive asynchronous discharges of Purkinje and granular cells, they said, would underlie the surface-negative deflection of the responses led from the vermis and crus II and the later component of the surface-negative potential led from crus I.

In interpreting the presently reported bipolar record taken with recording electrodes placed transversely across crus I, in which 2 unidirectional peaks appear, the one of shorter latency indicates afferent cerebellar inflow and the second is a measure of induced cerebellar firing.

SUMMARY

1. Cerebellar potentials are evoked by stimulation of the contralateral cerebral cortex, especially from the pericruciate region.

2. Potentials taken from crus II and the lateral aspects of crus I are usually surface-negative. Those taken from the medial and intermediate areas of crus I present a surface

positivity followed by a surface negativity.

3. The surface-negative potential is thought to reflect activity of neurons, the cell bodies of which are located in the cerebellar cortex. The surface-positive potential is considered to be indicative of conduction along pathways afferent to the cerebellum.

4. Records taken with bipolar electrodes oriented transversely across crus I display 2 prominent unidirectional peaks followed by a more prolonged after potential recorded in the opposite direction. Of these 2 peaks, the one of shorter latency reflects the afferent signal and the one of longer latency, along with the after potential, indicates evoked firing of cerebellar neurons.

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An evaluation of electroencephalography in cerebral infarction and ischemia due to arteriosclerosis

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DESPITE numerous reports on the electroencephalographic abnormalities in cerebrovascular disease, only a few studies have attempted to correlate the electroencephalographic findings with the location, duration, and size of cerebral infarction.[1,2] Several papers have been published on small groups of patients with isolated vascular syndromes, such as those caused by carotid artery,[3] middle cerebral,[4,5] or basilar artery thrombosis.[6–9] However, the serial changes developing throughout the course of cerebral infarction have received comparatively little attention.[1]

This report presents the electroencephalographic findings in 94 patients with evidence of cerebral thrombosis or infarction caused by arteriosclerosis. An attempt is made to correlate these findings with the site of the infarct, the severity of neurologic abnormalities, and the duration of the lesion. Particular attention is given to the evolving changes in the electroencephalogram occurring immediately after the infarction and during the ensuing weeks and months. On the basis of these observations, the usefulness of the electroencephalogram in the diagnosis and management of cerebral infarction is evaluated.

CASE MATERIAL AND METHODS

The case material in this study consisted of male patients in the Durham Veterans Administration Hospital who had clinical manifestations of cerebral infarction or recurrent cerebral ischemia. The etiology of the illness was considered to be atherosclerosis of the cerebral vessels in all but 1 patient, who was thought to have had a cerebral embolus. All patients with evidence of neurosyphilis or cerebral hemorrhage were excluded from the study. The ages of the patients ranged from 34 to 79 years, with an average age of 58. Hypertension, defined as consistent elevation of blood pressure of 150/100 mm. Hg or more was present in 38 of the patients. None of the patients had evidence of hypertensive encephalopathy. Azotemia, that is, blood urea nitrogen of more than 25 mg. per cent, was present in 9 patients; 5 others had diabetes. Autopsy examinations were made in 7 patients.

In 50 of the 94 patients, a neurologic examination was made by one of the authors at the time of each electroencephalogram. The electroencephalographic records in the remaining 44 patients were studied retrospectively, the patients having been examined by staff neurologists within the previous two years. Of the 94 patients, 73 were diagnosed as having infarction or ischemia of the cerebral hemispheres, with unilateral infarction in 48, bilateral in 18, and ischemia in 7. The remaining 21 patients had brain stem signs attributable to atherosclerosis of the vertebral-basilar artery system; 2 of these had ischemic attacks only.

The patients with unilateral infarction of the cerebral hemisphere were classified as to the severity of the infarction. Those manifesting considerable limitation of movement in one or

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more limbs were considered to have moderate to severe neurologic impairment; patients with minimal hemiparesis, monoparesis, or isolated central facial paralysis were classed as having mild neurologic dysfunction. The few patients with minimal weakness but severe sensory loss or visual field defect were considered to have moderate neurologic impairment; 6 patients whose major or sole deficit was aphasia were classed as having a mild impairment but are given separate consideration.

Electroencephalograms were made as soon as possible after the patient's admission and, when feasible, were repeated every week for three weeks and every month thereafter for at least three months. Among the 48 patients with unilateral hemispheral infarcts, 24 had electroencephalographic examinations a few hours to two weeks after onset; 15, from two to five weeks; and 25, more than five weeks. In the latter group, 8 patients had electroencephalographic records made within three months, 6 between three to six months, and 11 between six to eighteen months after the onset of their illness. A total of 64 electroencephalograms were taken in these 48 patients.

All the electroencephalograms were done on an 8-channel Grass Model III-D electroencephalograph, using both monopolar and bipolar recording technics and standard 10-20 electrode placements[10] (Figure 1*E*).

The electroencephalogram was considered normal if there was a dominant rhythm of 8 to 13 cycles per second without significant slow activity or asymmetries in voltage or frequency. Records showing predominantly low voltage fast activity below 15 μv. were also considered as normal.

RESULTS

Unilateral cerebral infarction. A diagnosis of unilateral infarction of the cerebral hemisphere was made in 48 patients. Of these, 30 patients (62.5%) had definite electroencephalographic abnormalities, 10 had borderline changes, and 8 had normal records. In the early stages of cerebral infarction, the electroencephalogram showed high voltage slow waves, usually in the delta frequencies. These were usually confined to the involved hemisphere, appearing diffusely in the frontal, central, and temporal areas. Suppression of the normal background electrical activity over the involved hemisphere was also a significant finding in acute infarction, being present in one-half of the patients with delta activity. The alpha rhythm on the side of the infarction was often slow, absent, poorly regulated, or mixed with slow waves.

Of these 30 patients, 7 had bilateral electroencephalographic changes; in only 4 were these sufficiently severe to make lateralization difficult. The electroencephalographic records in these 4 patients showed bilateral asymmetric slow waves without localizing signs, bilateral slow waves with potentiated background activity on the involved hemisphere, or slow waves on the uninvolved side with ipsilateral suppression of electrical activity. None of them had clinical evidence to suggest bilateral cerebral lesions.

In addition to these abnormalities, epileptiform sharp waves were seen in the temporal or posterior temporal areas in 5 patients; 2 of these had seizures at the onset of their cerebral infarction. Of the latter, 1 was thought to have had cerebral embolism and had recurrent seizures.

Most of the 10 patients with borderline electroencephalographic abnormalities showed random slow waves over the temporal areas. Other patients showed isolated theta waves over the involved area, with mild suppression of background rhythms, alpha asymmetry over the frontal areas, and focal ipsilateral potentiation of background activity during sleep. These changes were not considered sufficiently constant or severe to justify classifying the record as abnormal. The 8 patients with normal electroencephalographic records had various clinical manifestations; 2 had definite evidence of carotid thrombosis.

The patients with the more severe neurologic manifestations and presumably larger areas of infarction tended to have a higher incidence of electroencephalographic abnormalities. Thus, 23 (67.6%) of 34 patients with unilateral cerebral infarction and severe or moderate degrees of motor weakness had abnormalities, whereas only 7 of 14 patients with mild neurologic deficits showed such findings.

The duration of the cerebral infarction seemed to have little significant effect upon the incidence of electroencephalographic abnormalities (Table 1). Of the 24 patients in

TABLE 1
RELATION OF ELECTROENCEPHALOGRAPHIC FINDINGS TO DURATION OF UNILATERAL CEREBRAL INFARCTION
(64 electroencephalograms taken in 48 patients)

Duration of infarcts	Number of records	Interpretation of electroencephalograms		
		Abnormal	Borderline	Normal
Acute (< 2 weeks)	24	17(4)	5	2
Subacute (2 to 5 weeks)	15	9(1)	2	4
Chronic (5 weeks to 18 months)	25	17(2)	5	3
Total	64	43(7)	12	9

Figures in parentheses indicate number of records with marked bilateral abnormalities.

whom electroencephalographic examinations were made within two weeks after onset of infarction, 17 (70%) had definite abnormalities. Of 15 patients with electroencephalographic records taken two to five weeks after onset of cerebral infarction, 9 (60%) showed abnormalities, whereas 17 of 25 patients (68%) with studies made later than five weeks showed such changes. The abnormalities in the patients with longstanding infarction, however, differed from those found in patients with acute lesions. About one month after onset of infarction, the abnormalities usually became more focal in location and limited to the side of the lesion. In addition, the delta activity subsided and was replaced by low voltage theta frequencies. Suppression of the background activity over the ipsilateral hemisphere was also frequent in chronic lesions and was observed in 6 of the 17 abnormal electroencephalographic examinations.

Recurrent cerebral ischemic attacks. Of the 7 patients with transient cerebral ischemia involving branches of the internal carotid or middle cerebral arteries, 5 had normal and 2 had abnormal electroencephalographic records (Table 2). Of the 2 patients with abnormal records, 1 had over the involved hemisphere theta waves which were most pronounced in the temporal area. The other had a voltage asymmetry in alpha rhythm, with an increase in frontal alpha activity and a decrease in occipital alpha on the side of the lesion. An additional patient (Case 3, presented below) was admitted with ischemic attacks and also showed electroencephalographic abnormalities. He subsequently developed a cerebral infarction and is included in the 48 patients with unilateral cerebral infarction.

SERIAL STUDIES

The various electroencephalographic changes at the onset of the illness and their evolution in the course of unilateral cerebral infarction are described in the following case reports. Initially, the changes were confined to the involved hemisphere but occasionally they appeared bilaterally. After a period of a month or more, the slow activity in the electroencephalogram shifted from the delta to the

TABLE 2
INITIAL ELECTROENCEPHALOGRAPHIC FINDINGS IN 46 PATIENTS WITH VARIOUS CEREBROVASCULAR SYNDROMES

Cerebrovascular disease	Number of patients	Interpretation of electroencephalograms		
		Abnormal	Borderline	Normal
Transient ischemic attacks				
Carotid-middle cerebral vessels	7*	2	0	5
Vertebral-basilar vessels	2	0	1	1
Brain stem infarction				
Localized	13	1	0	12
Diffuse	6	5(4)	0	1
Bilateral infarction of cerebral hemispheres	18	16(13)	2	0

The figures in parentheses indicate numbers of patients with bilateral abnormalities.
*An additional patient (G.C.) had ischemic attacks with abnormal electroencephalogram on admission but subsequently developed cerebral infarction and is included in Table 1.

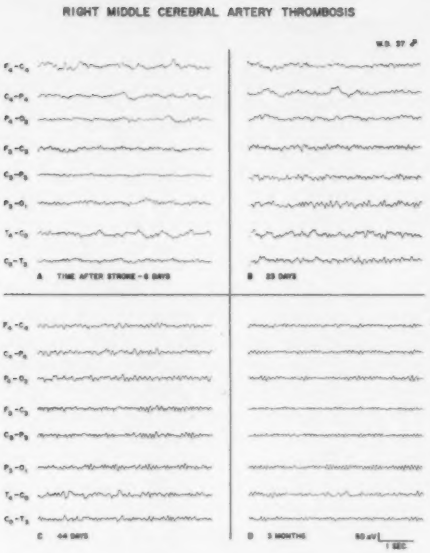


Fig. 1. *Case 1.* [A] Diffuse delta activity over right hemisphere. [B] Delta persists, but theta and delta now present on left. [C] Diffuse theta present on right, focal theta on left temporal area. [D] Theta on right temporal area, slow alpha on right.

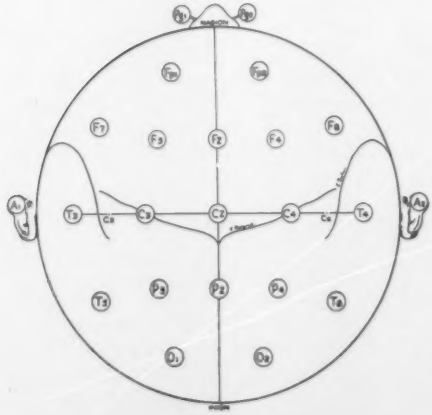


Fig. 1E. Diagram of the head showing electrode positions used in succeeding figures. (Electrode C_Z is referred to in the figures as C_O.)

theta range, with a reduction in voltage and a tendency to become more focal in location.

Case 1. This patient demonstrates typical electroencephalographic abnormalities associated with cerebral infarction. There was considerable restoration of neurologic function, but the electroencephalogram continued to show focal slow waves over the involved hemisphere.

W. D., age 37, a known hypertensive (blood pressure, 230/130), suddenly developed left hemiplegia, hemihypalgesia, and homonymous hemianopsia. The electroencephalogram taken six days after the onset showed marked delta and theta activity over the right hemisphere and absence of alpha rhythm over the right occipital area (Fig. 1*A*). After twenty-five days, the activity over the right hemisphere was unchanged but slow waves appeared over the left hemisphere (Fig. 1*B*), despite the general improvement in the patient's clinical picture. After forty-four days, the patient was able to walk with the aid of a cane but continued to have marked weakness of the left hand. The electroencephalogram at this time showed a decrease in the delta waves over the right hemisphere, with replacement by theta rhythm (Fig. 1*C*). After three months, the patient showed improvement in walking but continued to have moderate weakness of the left hand. The electroencephalogram also improved considerably, but theta waves persisted over the right temporocentral area, and a slower alpha rhythm was present over the right hemisphere (Fig. 1*D*).

Case 2. This patient demonstrates the presence of severe electroencephalographic abnormalities out of proportion to the clinical manifestations. Marked bilateral changes developed shortly after onset of infarction.

H. K., age 65, had sudden onset of a very mild right hemiparesis involving chiefly the hand. The electroencephalogram taken the following day showed considerable delta activity over the left hemisphere (Fig. 2*A*). Eight days after the onset, the patient's neurologic manifestations remained unchanged but the electroencephalogram had become considerably worse, with high voltage bilateral delta activity (Fig. 2*B*). Three months later, the patient had practically complete recovery. However, occasional theta and delta waves remained over the left frontotemporal area, with decreased voltage of the background rhythm present over this hemisphere (Figs. 2*C* and *D*).

Case 3. This case demonstrates the presence of electroencephalographic abnormalities in a patient with transient cerebral ischemic

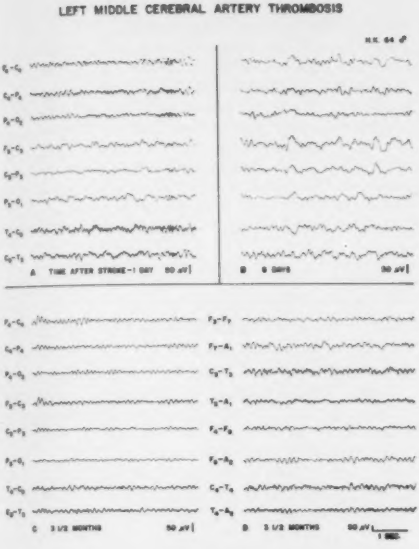


Fig. 2. *Case 2.* [A] Delta activity and suppression on left with 6- to 7-cps background on the right. [B] Bilateral delta with some synchronous bursts. [C] Moderate suppression of background rhythm on left. [D] Focal delta and theta, left frontotemporal area

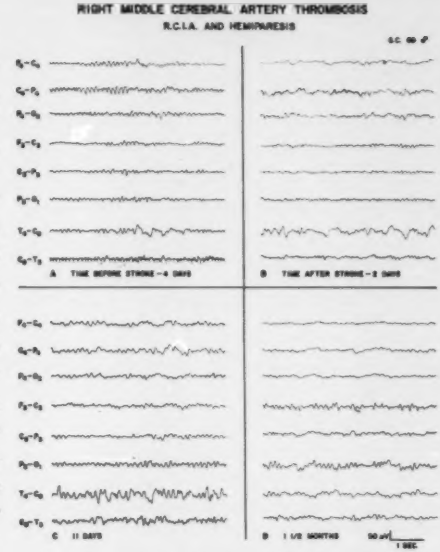


Fig. 3. *Case 3.* [A] Focal right temporal delta activity. [B] Diffuse delta on right, maximal in temporal area. [C] Delta and theta on right with left temporal theta. [D] Low voltage delta and theta on right

attacks who subsequently developed infarction with hemiparesis.

G. C., age 69, complained of transient weakness in the left arm and leg, approximately one minute in duration and occurring about twice daily during the five weeks before admission. He also had orthostatic hypotension with a 25% reduction in mean blood pressure in the erect posture, probably the result of a lumbar sympathectomy performed several years before.

On admission, the neurologic examination was completely normal but the electroencephalogram showed delta and theta waves in the right temporal and central areas (Fig. 3*A*). Four days later, the patient suddenly developed a moderate left hemiparesis, involving chiefly the upper extremity. The electroencephalogram taken two days afterward showed a definite increase in delta activity over the right hemisphere (Fig. 3*B*). After eleven days, the delta activity had developed sharper wave forms (Fig. 3*C*). The patient's clinical picture, however, was unchanged.

After one and one-half months, little improvement was noted in the neurologic deficit. The electroencephalogram at this time showed suppression of background rhythm and low voltage theta and delta activity over the right hemisphere (Fig. 3*D*). No further recovery of function or changes in the electroencephalogram were observed five months after the onset of the illness.

Case 4. This case demonstrates bilateral electroencephalographic changes associated with cerebral edema and vascular occlusion. There was complete resolution of the severe hemiparesis, but focal abnormalities remained.

H. B., age 45, had sudden severe left hemiparesis followed within a few hours by a seizure. He became stuporous and showed Cheyne-Stokes respiration. The presence of cerebral edema was indicated by increased spinal fluid pressure (330 mm.) and a pineal shift in the skull roentgenograms.

The initial electroencephalogram obtained twelve days after onset showed potentiated alpha rhythm over both frontal areas, particularly on the right. Sinusoidal delta waves and occasional theta waves were also present over the right hemisphere. Mixed theta and delta rhythms were present on the left but were generally of lower voltage (Fig. 4*A*).

Nineteen days after onset of illness, the patient showed some return of motor function but continued to be somnolent with occasional periods of

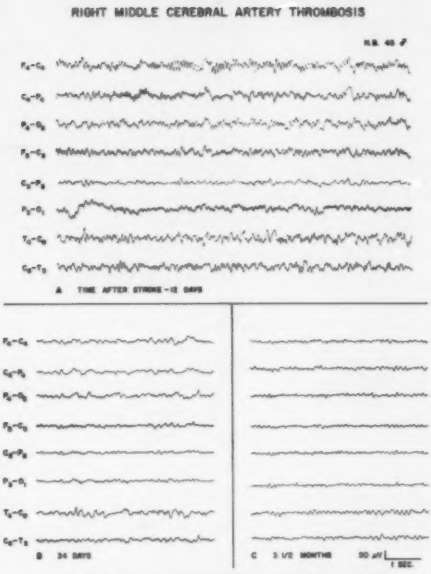
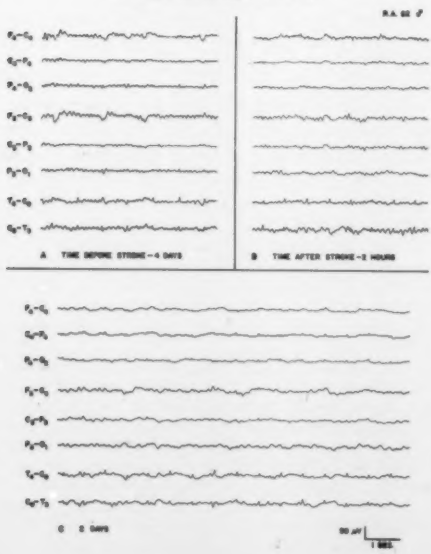


Fig. 4. *Case 4.* [A] Bilateral delta and potentiated alpha, most marked on the right. [B] Delta on the right, with low voltage, poorly regulated background on left. [C] Focal theta, right central and temporal area



◀ Fig. 5. *Case 5.* Massive right hemisphere infarction. [A] Poorly regulated alpha bilaterally. [B] Moderate suppression on right with random delta and theta on left. [C] Bilateral suppression of background with low voltage delta and theta on right, higher voltage on left

lucidity. The electroencephalogram at this time showed low voltage fast rhythms in both hemispheres, with low voltage theta and delta rhythms over the right hemisphere. After thirty-four days, the mental confusion had cleared and only minimal motor weakness remained. The electroencephalogram at this time continued to show diffuse theta and delta waves over the right hemisphere (Fig. 4*B*). No neurologic deficit was apparent three and one-half months after onset of illness, but focal theta activity remained over the right temporal region (Fig. 4*C*).

Case 5. This case illustrates the suppression of electroencephalographic activity in a patient with severe hemiparesis, with coma and rapid progression to death.

R. A., age 62, had a history of chronic hypertension and mental confusion. Two weeks before admission, he had transient loss of consciousness with left-sided weakness. The electroencephalogram taken on admission was normal with poorly regulated alpha rhythm bilaterally (Fig. 5*A*). Four days later, the patient suddenly lost consciousness and had a left hemiplegia. The electroencephalogram two hours later showed suppression of the background activity of the right hemisphere with theta and delta activity in the left central and temporal areas (Fig. 5*B*). The patient remained comatose, with no improvement in motor strength. The electroencephalogram two days after onset of hemiplegia showed absence of normal background activity bilaterally, with low voltage rolling delta waves over the right hemisphere and higher voltage theta and delta activity over the left hemisphere (Fig. 5*C*). The patient died the following day. Autopsy revealed a massive infarction with marked edema in the right cerebral hemisphere.

APHASIA

In this study, 6 patients had aphasia as their chief or only persistent neurologic defect; 5 of these had abnormal electroencephalographic records with slow activity occurring mainly over the left temporal, parietal, and central areas. The 1 normal record was made two months after an episode of transient aphasia. The focal nature of the abnormalities that occurred in association with aphasia is demonstrated in Figure 6.

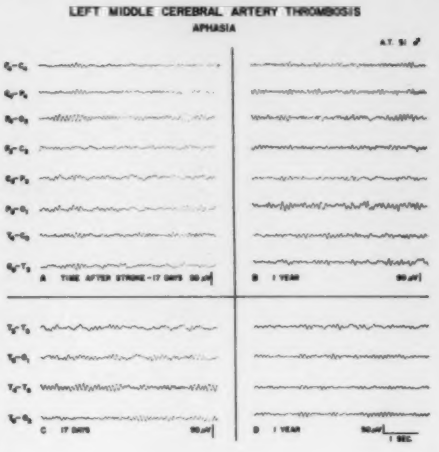


Fig. 6. A. T., age 51, with receptive aphasia. [A] Low voltage delta most marked over left posterior head areas. [B] Poorly regulated background with moderate suppression over left centroparietal area, with random temporal delta. [C] and [D] Early and persistent focal delta in left posterotemporal area. Partial auditory receptive aphasia is still present, but alexia and agraphia have completely cleared.

BILATERAL CEREBRAL INFARCTION

Evidence of infarction of both cerebral hemispheres was present in 18 patients (Table 2); 13 of them had definite histories or neurologic evidence of bilateral motor or sensory impairment, whereas 5 showed mental deterioration and pseudobulbar palsy with unilateral motor weakness. Of these 18 patients, 16 had abnormal electroencephalographic records that could be grouped into 4 relatively distinct types. In 3 patients, the abnormalities consisted of generalized bilateral synchronous delta and theta activity suggesting a subcortical lesion (Fig. 7*A*). These 3 patients had histories of recent cerebral thrombosis and showed bilateral motor signs and mental deterioration without loss of consciousness.

The second group of abnormalities consisted of bilateral suppression of all electrical activity (Fig. 7*B*). This finding was present in 3 patients, 1 of whom was comatose, the other 2 had their last cerebral vascular episodes four months or more before electroencephalographic examination.

The third type of abnormality was noted in 7 patients and appeared as either asymmetric bilateral theta and delta activity or slow waves over one hemisphere with suppression of background activity over the other hemisphere (Fig. 7*C*). The fourth type of abnormality, appearing in 3 patients, consisted of unilateral theta or delta activity with normal electroencephalographic activity over the opposite hemisphere (Fig. 7*D*). In these 10 patients, there was no constant relationship between the side of the recent infarction and the site of the maximal slow activity.

The 2 patients with borderline electroencephalographic abnormalities had pseudobulbar palsy with unilateral limb involvement.

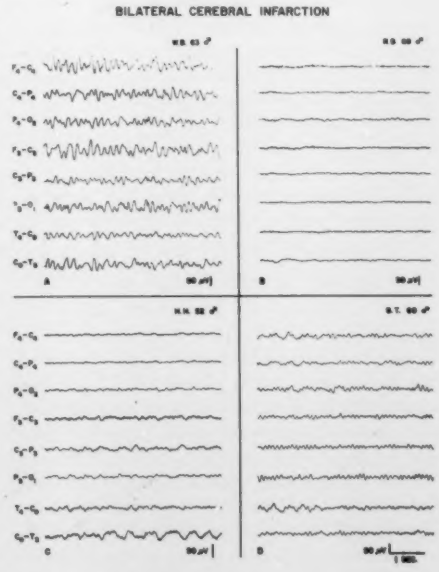


Fig. 7. Bilateral cerebral infarction. [A] Bilateral synchronous delta and theta. [B] Bilateral suppression of background. [C] Bilateral abnormalities with suppression on the right and slowing on the left. [D] Unilateral abnormalities with delta and theta on the right

TABLE 3
CORRELATION BETWEEN CLINICAL, ELECTROENCEPHALOGRAPHIC, AND POSTMORTEM FINDINGS

Patient	*Clinical data*	*Time after stroke*	*Electroencephalographic chanbes*	*Time after EEG*	*Postmortem findings*
R.M.	Left hemisensory defect and hemiparesis	3 days	Random delta and theta: Right central, temporal, and parietal areas	3 days	Infarct: Right parietal lobe, insula, and optic radiation
W.McD.	Mixed aphasia	12 days	Delta: Left central, temporal, and parietal areas	6 mo.	Infarcts: Left parietal cortex (6 x 4 x 0.7 cm.), right parietal cortex (1.5 cm.)
A.S.	Left hemiparesis, hemianopia and cortical sensory loss, progressed to hemiplegia after 4 days	13 days	Asymmetric bilateral delta and theta. Right background suppressed	2 days	Massive infarct: Right parietal and temporal lobes, insula, and basal ganglia
J.C.	4 years before: Left hemiparesis; present admission: right hemiplegia and coma	3 days	Background suppressed, bilaterally. Random delta	8 days	Old massive infarct: Right occipital and temporal lobes. Recent infarct: Left internal capsule and basal ganglia, patchy cortical necrosis, and cerebral edema
R.P.	2 years before: Mixed aphasia	9 days	Delta: Left temporal, parietal, and central areas	2½ yr.	Small infarct: Left superior temporal and supramarginal gyri
	Present admission: Left hemiplegia, confusion	20 days	Background activity absent on right. Theta and delta: Left posterior head areas	6 mo.	Massive infarct: Right frontal, temporal, and parietal lobes
S.P.	2 years before: Right hemiplegia; present admission: Left hemiplegia	6 mo.	Sporadic random low voltage delta: Left hemisphere	6 mo.	Infarcts: Left parietal occipital cortex, left internal capsule, and caudate nucleus. Multiple small infarcts bilaterally, frontal lobes

POSTMORTEM STUDIES

The correlation among the clinical, electroencephalographic, and autopsy findings in 6 patients is summarized in Table 3 and Figures 8 and 9. There were 3 patients (R.M., W.M., and S.P.) with infarctions of small or moderate size. All had ipsilateral slow activity in their electroencephalographic records. The 3 patients with massive hemispheral infarcts (A.S., J.C., and R.P.) had suppression of normal background activity over the involved hemisphere with a variety of changes present over the opposite hemisphere.

THROMBOSIS OF VERTEBRAL-BASILAR VESSELS

In 21 patients with brain-stem lesions, all of whom had an electroencephalogram made within two weeks after onset of symptoms, 36 records were made. Of these 21, 13 had small, well localized brain stem infarctions, 2 had recurrent ischemic attacks, and 6 had diffuse brain stem manifestations (Table 2). Of the 13 patients with localized lesions, 7 had infarction of the lateral medullary plate. The remaining 6 showed isolated signs such as unilateral abducens palsy, internuclear or supranuclear ophthalmoplegia, and combined fifth and seventh cranial nerve lesions. Only 1 of these 13 patients had an abnormal record. This occurred in a patient with supranuclear ophthalmoplegia and mild azotemia (blood urea nitrogen, 30) who showed bilateral synchronous theta waves of 6 to 7 cycles per second.

Of the 2 patients with basilar insufficiency and mild residual neurologic deficits, 1 showed borderline changes with slow waves over the left temporal area and the other had a normal record.

The 6 patients with diffuse brain stem involvement had episodes of quadriparesis, ataxia, incoordination, bilateral Babinski signs, dysphagia, and dysarthria in a variety of combinations. Definite localization of the lesion within the brain stem was not possible, but they seemed to have pontomedullary involvement rather than more rostral lesions. All but 1 had an abnormal electroencephalogram. The electroencephalographic abnormalities in these 5 patients usually consisted of bilateral theta and delta waves of varying synchrony appearing over all head areas but predomi-

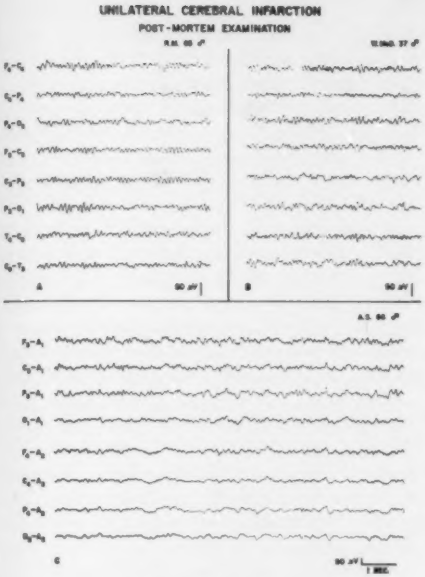


Fig. 8. Unilateral cerebral infarction. [A] Theta and delta on right most marked over posterior head areas with moderate sized right parietal lobe infarct. [B] Focal delta over left central, temporal, and parietal areas with small left temporoparietal infarct. [C] Bilateral delta with suppression on the right with massive right hemisphere infarction

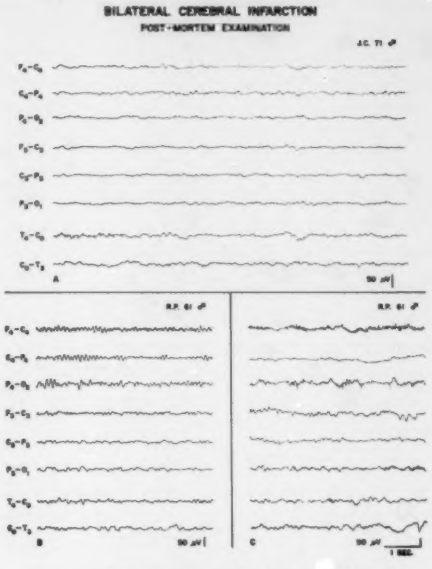


Fig. 9. Bilateral cerebral infarction. [A] Bilateral suppression of background activity with low voltage theta and delta. [B] Delta activity over posterior head areas on left nine days after onset of aphasia. [C] Suppression of background activity on the right, with theta and delta on the left still most marked over the posterior head areas after recent massive right hemisphere infarction

nantly in the occipital and temporal areas; 3 showed sharp waves in the temporal areas. These abnormalities tended to become minimal in the chronic period. None of the 5 patients were comatose, but 3 were confused; 1 of the patients with marked bilateral abnormalities had severe azotemia.

Case 6. This patient demonstrates typical electroencephalographic findings associated with diffuse pontomedullary involvement.

S.T., age 60, for two months had weekly episodes of vertigo, visual blurring, dysphagia, and dysarthria, lasting twenty minutes to an hour. On admission, the patient was confused and showed dysarthria, ataxic gait, and right facial weakness. An electroencephalogram made four years before was normal. The first electroencephalogram obtained a week after admission showed bilateral generalized theta activity with occasional delta waves (Fig. 10*A*). Nine days after admission, the right hemisphere was more abnormal, with generalized slow activity most pronounced posteriorly (Fig. 10*B*). Sixteen days after onset, the dysarthria had cleared and the gait had improved. The electroencephalogram at this time continued to show bilateral theta waves, with delta waves on the right (Fig. 10*C*). Four weeks after the onset, the electroencephalogram had considerably less slow activity. Four months later, the electroencephalogram showed only occasional theta waves over the right parietooccipital area (Fig. 10*D*).

DISCUSSION

The results of this study indicate the value and limitations of electroencephalography in the diagnosis of cerebral infarction. A major drawback in the practical use of electroencephalography in this disorder is the fact that only 62% of the patients with evidence of unilateral cerebral infarction had definite electroencephalographic abnormalities. It is possible that some of these patients with normal electroencephalograms actually had infarction

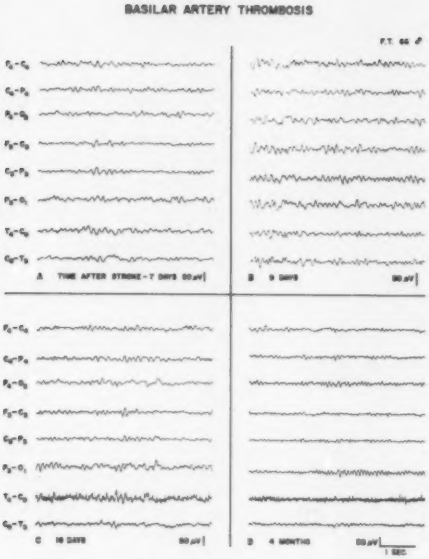


Fig. 10. *Case 6.* Basilar artery thrombosis. [A] Bilateral, usually asymmetric theta activity. [B] Bilateral theta and delta with slower waves on the right in the occipital area. [C] Bilateral theta and delta activity most marked in the posterior head areas, particularly on the right. [D] Occasional theta right parietooccipital area

in the brain stem, but the neurologic findings did not support this diagnosis. Moreover, 2 of them were found to have evidence of carotid occlusion on arteriography. Roseman[1] and others[11] have suggested that patients with cerebral thrombosis and normal electroencephalographic findings may have small subcortical infarctions in or near the internal capsule. This possibility must remain speculative, since the exact site of such lesions cannot be determined by clinical methods.

The electroencephalographic abnormalities in many of our patients during the acute period did not correlate well with the specific site or severity of the infarction as determined clinically nor were they consistently related to the degree of recovery. Lateralization of the involved hemisphere, using slow activity as a criterion, however, was correct in all but a few patients. Severe massive infarctions were often associated with low amplitude delta activity or diffuse suppression of the electrical activity over the affected hemisphere. High voltage slow waves seemed to be associated with more localized lesions. Several of our patients with unilateral circumscribed motor or sensory findings had electroencephalographic abnormalities that were either distributed diffusely over the involved hemisphere or occurred bilaterally. In some instances, the abnormalities became worse within the first few weeks after the development of the infarct without corresponding change in the patient's clinical picture. After three to four weeks, however, the electroencephalographic changes tended to become localized and corresponded roughly with the suspected area of infarction.

The finding of suppression of normal electrical activity over the area of massive infarction and focal slow waves about the site of smaller cortical infarcts had been observed in animals with experimental infarction.[12] The bilateral electroencephalographic changes occurring in the acute period of infarction have also been noted experimentally and have been thought due to damage of midline structures.[13] The diffuse transient electroencephalographic abnormalities that involve most of the hemisphere are generally considered caused by edema or perhaps by involvement of areas that do not produce clinical manifestations.[1,2] This lack of correlation between the neurologic findings and the electroencephalographic abnormalities has been emphasized by Hill,[14] who states that such relationships cannot always be made, since electroencephalographic activity is sensitive to structural lesions as well as to physiochemical changes often remote from the areas under observation. Consideration of these factors would explain some of the apparent inconsistencies in this study.

The interpretation of the electroencephalogram in cerebral infarction is often complicated by the presence of electroencephalographic abnormalities in the temporal areas, which are frequently seen in normal elderly individuals.[15] Moreover, patients with cerebrovascular disease may have associated uremia,[16] epileptic seizures, or hypertensive encephalopathy, all of which may produce electroencephalographic changes. On the other hand, only one-third or less of patients with recurrent transient cerebral ischemic attacks showed

electroencephalographic abnormalities. Previous reports on transient ischemic attacks due to carotid artery insufficiency showed that one-half of the patients had abnormal electroencephalograms.[17] Many of these had minor changes in the temporal areas, which, as mentioned above, are without apparent pathologic significance.

As would be expected, patients with severe bilateral cerebral hemisphere infarcts had the most abnormal electroencephalograms, consisting of bilateral slow waves, suppression of electrical activity, or slow waves over one hemisphere with suppression over the other. The electroencephalograms in these patients may be similar to those of patients with diffuse brain stem lesions. In the latter group of patients, temporal sharp waves appear more frequently. Patients with isolated pontine or medullary involvement or with small, well localized mesencephalic lesions frequently had normal records, indicating that these infarcts may have been located caudal or lateral to the reticular substance of the tegmentum of the mesencephalon. This area is now considered to have significant influence in the regulation of the electroencephalogram.[18]

Despite the actual and theoretic limitations of electroencephalography in cerebral infarction, we feel that this technic has several useful applications. The electroencephalogram may be used to confirm the suspected site of the infarct. If unilateral abnormalities are present, it is supportive evidence that the vessels of the internal carotid system are involved and not primarily those of the vertebral-basilar system. Conversely, a normal electroencephalogram in cerebral infarction is more likely to be associated with a localized brain stem lesion than with hemispheral involvement. Bilateral synchronous slow activity, often with temporal sharp waves, is more frequently associated with diffuse brain stem lesions than with bilateral cerebral infarctions. Persistence of bilateral electroencephalographic changes for weeks or months indicates the presence of bilateral cerebral infarcts. The electroencephalogram may also be used to determine cerebral dominance in sinistrals with aphasia as the only symptom.

Serial electroencephalographic studies may provide some indication of the prognosis as well as the state of resolution of the ischemic process. Patients continuing to show diffuse abnormalities more than a month after the onset of the infarction seemed to have greater neurologic deficits than those with focal changes. Half of the patients with old infarcts and abnormal electroencephalograms showed diffuse slow activity and had at least moderate residual motor weakness. The remaining half had focal abnormalities and showed only mild or no residual neurologic signs, even though there was often moderate or severe impairment at onset.

During the course of the infarction, an evolving electrical pattern of altered neuronal activity may appear. In acute infarction, there is typically high voltage delta activity, either involving a considerable portion of the ipsilateral hemisphere or relatively limited to the area about the infarction. These abnormalities may become worse in the first few days, and slow waves may appear diffusely over the ipsilateral hemisphere or the contralateral hemisphere. The delta activity usually subsides but may remain for many months. Eventually, it is replaced by theta waves. Suppression of the normal background activity over the involved hemisphere remained in approximately one-third of the patients.

SUMMARY

A study was made in 94 patients of the electroencephalographic changes associated with cerebral infarction due to arteriosclerosis. Only two-thirds of patients with a diagnosis of unilateral infarction in the cerebral hemisphere had lateralizing electroencephalographic abnormalities. Definite abnormalities were usually absent in patients with small, localized brain stem lesions and in patients with intermittent cerebral ischemia. Diffuse brain stem infarction or bilateral hemispheral lesions were associated with a high incidence of electroencephalographic abnormalities. Close correlation between the electroencephalographic findings and the site and severity of the neurologic deficit was not observed. Serial electroencephalographic studies demonstrated a relationship between the pattern of electrical activity and the state of resolution of the pathologic process in the individual patient.

We are indebted to Mrs. Margaret Rosett for her technical assistance in the study.

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Relationship of differential electroencephalographic patterns to distribution of Wechsler-Bellevue scores

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THE RELATIONSHIP between electroencephalographic patterns and personality parameters has been the subject of a great number of studies over the years. However, relatively few studies have been done on electroencephalographic patterns and their relationship to varying intellectual abilities.

This study was undertaken to determine a possible differential effect of brain damage on the Wechsler-Bellevue scale when the groups were composed according to electroencephalographic criteria. The patients tested also had been given the Halstead neuropsychologic battery, which permitted a comparison of Halstead's impairment index and the distribution of Wechsler-Bellevue scores.

Birren[1] and Cohen[2] have independently published factorial analyses of the Wechsler-Bellevue scale. They both found factors composed of verbal subtests only and of performance subtests only. Reitan[3] demonstrated recently that a definite relationship exists between the distribution of Wechsler-Bellevue scores and lateralized cerebral lesions. Also, Kløve and Reitan[4] found a striking relationship between the distribution of Wechsler-Bellevue scores and the presence of dysphasia or spatial distortion.

Since both the Wechsler-Bellevue scale and electroencephalography are routine examinations, further investigation of the relationship of these 2 diagnostic methods seemed of value.

MATERIAL AND METHODS

In this study, 185 patients with verified brain damage were examined. The patients represent general referrals for neuropsychologic examination from the neurologic and neurosurgical services at Indiana University Medical Center. The patients were divided, according to electroencephalographic criteria, into 4 groups which were not statistically different with respect to age, education, and time elapsed between the psychologic examination and the electroencephalogram. Results on these variables are presented in Table 1.

Group I consisted of 37 patients whose electroencephalograms showed maximal abnormal activity over the right hemisphere; group II, 42 patients with electroencephalograms showing maximal abnormal activity over the left hemisphere; group III, 45 patients whose electroencephalograms showed generalized abnormal activity over both hemispheres; and group IV, 61 patients with brain damage but with normal electroencephalograms.

The following circumstances would exclude a patient from the study: left handedness, incomplete testing, or surgery between psychologic testing and electroencephalograms. This last provision was made in order to keep the patients' conditions as similar as possible at the time of the 2 examinations.

The Wechsler-Bellevue Scale of Adult Intelligence (Form I) and the Halstead battery were administered to each patient and scored completely before any of the groups were composed. No attempt was made to select patients with respect to such variables as localization, extent, or type of lesion. While these factors may be relevant to the results

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TABLE 1
DESCRIPTIVE VARIABLES FOR EACH OF THE 4 GROUPS

	N	Sex	Mean age	S.D.	Range	Mean educ.	S.D.	Range	Mean time diff.*	S.D.	Range
Group I											
EEG abnormality maximized over right hemisphere	37	4F33M	35.71	12.71	15-62	10.73	2.97	5-19	0.97	1.99	0-4
Group II											
EEG abnormality maximized over left hemisphere	42	9F33M	37.00	14.10	15-71	9.69	3.13	6-16	1.69	3.19	0-14
Group III											
EEG abnormality generalized over both hemispheres	45	11F34M	31.97	9.78	16-58	9.78	3.20	2-17	1.84	5.04	0-29
Group IV											
Normal EEG	61	10F51M	33.89	11.37	15-59	10.75	3.24	4-20	1.39	2.95	0-16

*Mean time difference refers to time in months elapsed between the psychologic examination and the electroencephalogram.

obtained, the design of the present study does not permit their evaluation. The diagnostic categories for the groups are shown in Table 2.

The electroencephalographic information was taken directly from the electroencephalographer's clinical report for each patient. No reevaluation was made, since it was felt that the study would be more meaningful when routine clinical reports were used as a basis for composing the groups.

An 8-channel Grass electroencephalograph, model IIIA, was used in obtaining the records. Bipolar recording technic with 14 electrodes was used. Each patient was hyperventilated for three minutes, and photic stimulation was employed.

RESULTS

Means and standard deviations on Wechsler-Bellevue variables and Halstead's impairment index for the 4 groups are given in Table 3, which indicates that group I (electroencephalographic abnormality maximized over right hemisphere) had a mean verbal weighted score 10.62 points higher than its performance weighted score, group II (electroencephalographic abnormality maximized over left hemisphere), 6.41 points lower; group III (electroencephalographic abnormality generalized over both hemispheres), 0.47 points higher; and group IV (normal electroencephalogram), 0.20 points higher. The mean I.Q.'s consequently show the same relative differences. Hal-

TABLE 2
NUMBER OF PATIENTS IN DIAGNOSTIC CATEGORIES FOR EACH GROUP

Diagnosis	Group I	Group II	Group III	Group IV
Abscess	2	2	1	
Acoustic neurinoma	1			
Chronic brain lesion	4	5	11	17
Cerebral vascular accident	1	5		2
Epilepsy	3	12	14	10
Head Injuries				
Penetrating	9	2		4
Closed	3	1	5	3
Multiple sclerosis		3	7	23
Subdural hematoma		1		
Tumors				
Extrinsic	2	1	1	1
Intrinsic	9	9	6	
Vascular malformation	3	1		1
Total	37	42	45	61

TABLE 3

MEANS AND STANDARD DEVIATIONS OF WECHSLER-BELLEVUE VARIABLES AND THE IMPAIRMENT INDEX FOR EACH GROUP

	Group I		Group II		Group III		Group IV	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Inf.	10.19	2.24	8.10	3.21	8.49	4.17	9.92	2.73
Comp.	10.08	3.13	8.52	3.64	8.55	3.93	10.03	2.86
Dig. sp.	7.35	3.50	5.00	2.84	7.58	4.00	8.01	3.90
Arith.	8.27	4.29	5.81	3.89	8.27	5.59	8.77	4.86
Simil.	9.49	3.15	7.83	3.59	8.15	3.99	9.67	3.23
Vocab.	9.62	3.08	7.62	3.60	8.09	4.01	9.80	2.81
Pict. arr.	6.54	3.05	7.86	3.36	7.49	3.57	8.47	3.52
Pict. comp.	8.14	4.14	8.52	3.27	8.07	3.96	10.08	3.73
Block des.	6.22	3.34	9.05	3.44	8.62	3.68	9.64	3.88
Obj. assem.	7.81	3.96	9.52	3.24	9.42	2.94	9.74	3.25
Dig. symb.	6.05	3.15	6.71	2.74	6.58	2.95	8.28	3.46
VWS	45.38	12.21	35.26	13.19	40.64	19.06	46.40	13.85
PWS	34.76	14.29	41.67	13.09	40.17	14.12	46.20	14.56
Total WS	80.14	22.69	76.93	24.50	80.81	31.49	92.60	25.99
V. I.Q.	99.79	13.85	88.43	16.00	93.46	22.19	100.75	16.23
P. I.Q.	87.82	18.35	98.43	16.99	93.15	18.51	102.62	17.84
Full sc. I.Q.	93.88	15.62	92.69	17.04	92.61	21.48	101.88	16.84
VWS minus PWS	10.62	12.70	−6.41	9.88	0.47	11.54	0.20	11.52
Imp. index	.65	.18	.70	.24	.63	.22	.61	.27

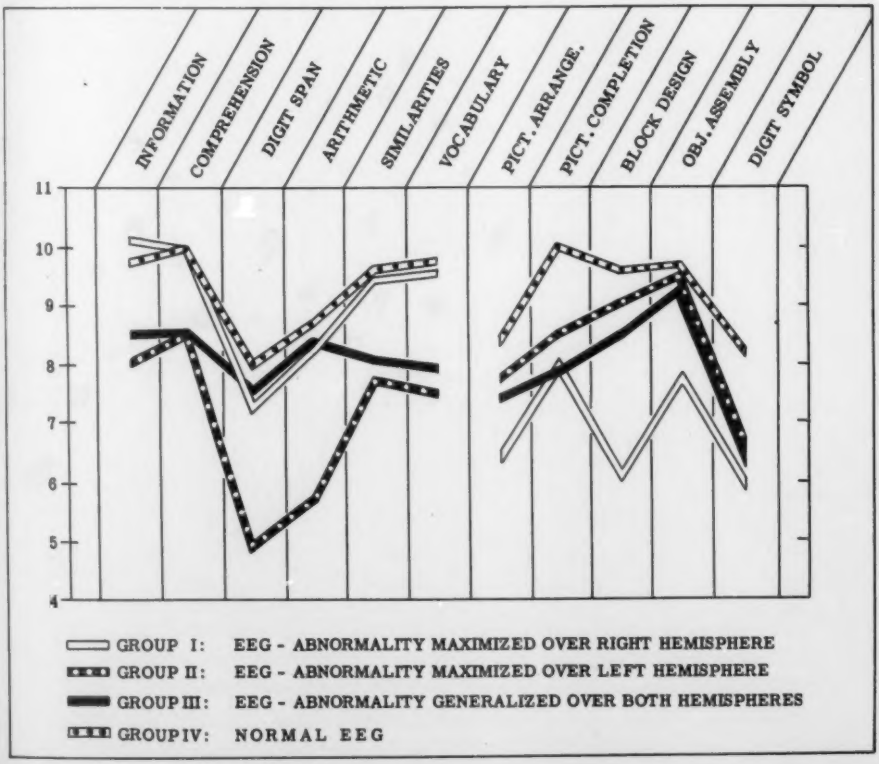

TABLE 4

MEAN DIFFERENCES BETWEEN WECHSLER-BELLEVUE VARIABLES AND IMPAIRMENT INDEX FOR EACH PAIR OF GROUPS AND THEIR LEVELS OF STATISTICAL SIGNIFICANCE

	Group I minus group II	*Group I minus group III*	*Group I minus group IV*	*Group II minus group III*	*Group II minus group IV*	*Group III minus group IV*
Information	2.09	1.70	0.27	−0.39	−1.82	−1.43
Comprehension	1.56	1.53	0.05	−0.03	−1.51	−1.48
Digit span	2.35	0.17	−0.66	−2.18	−3.01	−0.83
Arithmetic	2.46	0.00	−0.50	−2.46	−2.96	−0.50
Similarities	1.66	1.34	−0.18	−0.32	−1.84	−1.52
Vocabulary	2.00	1.53	−0.18	−0.47	−2.18	−1.71
Picture arrangement	−1.32	−0.95	−1.93	0.37	−0.61	−0.98
Picture completion	−0.38	0.07	−1.94	0.45	−1.56	−2.01
Block design	−2.83	−2.40	−3.42	0.43	−0.59	−1.02
Object assembly	−1.71	−1.61	−1.93	0.10	−0.22	−0.32
Digit symbol	−0.66	−0.53	−2.23	0.13	−1.57	−1.70
VWS	10.12	4.74	−1.02	−5.38	−11.14	−5.76
PWS	−6.91	−5.41	−11.44	1.50	−4.53	−6.03
Total WS	3.21	−0.67	−12.46	−3.88	−15.67	−11.79
Verbal IQ	11.36	6.33	−0.96	−5.03	−12.32	−7.29
Performance IQ	−10.61	−5.33	−14.80	5.28	−4.19	−9.47
Full scale IQ	1.19	1.27	−8.00	0.08	−9.19	−9.27
VWS minus PWS	18.22	10.15	10.42	−6.88	−6.61	0.27
Impairment index	−.05	0.02	0.04	0.07	0.09	0.02

LEVELS OF SIGNIFICANCE

	Group I minus group II	*Group I minus group III*	*Group I minus group IV*	*Group II minus group III*	*Group II minus group IV*	*Group III minus group IV*
Information	.01	.05	n.s.	n.s.	.01	.05
Comprehension	.05	n.s.	n.s.	n.s.	.01	.05
Digit span	.01	n.s.	n.s.	.01	.01	n.s.
Arithmetic	.01	n.s.	n.s.	.01	.01	n.s.
Similarities	.05	n.s.	n.s.	n.s.	.01	.05
Vocabulary	.01	n.s.	n.s.	n.s.	.01	.05
Picture arrangement	n.s.	n.s.	.05	n.s.	n.s.	n.s.
Picture completion	n.s.	n.s.	.05	n.s.	.01	.01
Block design	.01	.01	.01	n.s.	n.s.	n.s.
Object assembly	.05	.05	.05	n.s.	n.s.	n.s.
Digit symbol	n.s.	n.s.	.01	n.s.	.01	.01
VWS	.01	n.s.	n.s.	n.s.	.01	n.s.
PWS	.05	n.s.	.01	n.s.	.05	.05
Total WS	n.s.	n.s.	.05	n.s.	.01	.05
Verbal IQ	.01	n.s.	n.s.	n.s.	.01	n.s.
Performance IQ	.01	n.s.	.01	n.s.	n.s.	.01
Full scale IQ	n.s.	n.s.	.05	n.s.	.01	.05
VWS minus PWS	.01	.01	.01	.05	.01	n.s.
Impairment index	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

stead's impairment index gave only small differences between groups. A graphic representation of the comparative performances on the Wechsler-Bellevue subtests is presented in the illustration.

In Table 4, the mean differences between Wechsler-Bellevue variables and Halstead's impairment index and their level of statistical significance are presented.

Comparisons of groups I and II showed significant differences on both the verbal and performance weighted score means. Group I had the higher value for the verbal weighted score and group II, for the performance weighted score. The difference between the verbal weighted scores for these groups was significant beyond the 0.01 level of confidence and for the performance weighted scores beyond the 0.05 level of confidence. There was, however, no significant difference between the total weighted scores for these 2 groups.

On the individual subtests, too, groups I and II were generally significantly different. On the verbal subtests, group I had the higher means in each instance, and, on the performance subtests, group II consistently had the higher means.

Groups I and III were not significantly different with respect to verbal, performance, and total weighted scores. However, on the indi-

vidual subtests, significant differences between information, block design, and object assembly were present, with the higher scores occurring in group I for the verbal subtest and in group III for the performance subtests.

A comparison of groups I and IV revealed statistically significant differences for the performance subtests but no differences for the verbal subtests. Where differences occurred, the scores for group IV were higher. The performance and full scale weighted scores were significantly different for these 2 groups, while no difference was demonstrated for verbal weighted scores.

No significant differences between groups II and III were found, except on 2 verbal subtests, digit span and arithmetic, with the means for group III being the highest in each instance.

Groups II and IV were significantly different beyond the 0.01 level of confidence on all verbal subtests and on picture completion and digit symbol in the performance scale. The total weighted scores in groups II and IV also were significantly different.

Comparing groups III and IV, we found significant differences on information, comprehension, similarities, and vocabulary in the verbal scale and for picture completion and digit symbol in the performance scale. Verbal weighted scores just failed to be significantly different, while performance weighted scores and total weighted scores were different. In all instances, the means for group IV were the higher in this comparison.

The difference between verbal and performance weighted scores was computed for each group. This yielded significant differences in comparison between all groups except III and IV. Intergroup differences for Halstead's impairment index could, in each comparison, be attributed to chance.

COMMENT

Group I, composed of patients with electroencephalographic abnormalities maximized over the right hemisphere, was clearly impaired on the performance subtests of the Wechsler-Bellevue scale, and group II, consisting of patients with electroencephalographic abnormalities maximized over the left hemisphere, was impaired on the verbal subtests. Group III, composed of patients with generalized and nonlateralized electroencephalographic abnormalities, and group IV, composed of patients with normal electroencephalographic tracings, failed to demonstrate differences between the verbal and performance scales.

Other studies have been concerned with the relationship of electroencephalographic patterns to abilities,[5–7] but in none of these studies have electroencephalographic criteria been used for composing the groups. Thus, the results are not directly comparable to those of this study.

Vislie and Henriksen[8] found a mean I.Q. of 100 (Ravens Progressive Matrices) in patients without diffuse electroencephalographic dysrhythmia as opposed to a mean I.Q. of 89 in patients with diffuse dysrhythmia, but a comparison with our results is hardly legitimate because they used a selected group of patients (epileptics) and different measuring instruments.

It is important to notice that group IV, with normal electroencephalograms but definite brain damage, obtained a mean full scale I.Q. of 101.88, while the I.Q.'s for the 3 other groups ranged from 8.00 to 9.27 points lower. It appears from our findings that Wechsler-Bellevue results are not likely to reflect impairment in brain damaged patients with normal electroencephalograms. However, Halstead's impairment index fails to show any significant differences between the groups; all 4 groups vary between 0.61 and 0.70. In investigations by Halstead[9] and Reitan,[10] impairment indexes in this range definitely are characteristic of groups with established brain damage. This study was not designed to investigate the validity of Halstead's impairment index, but these findings may indicate it is more sensitive to the organic condition of the brain than are the electroencephalogram and Wechsler-Bellevue scale. That the index fails to differentiate between groups composed according to the criteria used in this study may be due to the relatively large number of different abilities represented in the index. A comparison of the individual tests on which the index is based would, however, be likely to reveal certain differences.

A comparison of the results of this study with those of Reitan[3] and Kløve and Reitan[4]

reveals a rather striking similarity in the general pattern of the mean distributions when the graphic presentations are inspected. Although different criteria for composing the groups have been used in these studies, they all represent criteria from which certain inferences might be made concerning lateralization of cerebral lesions.

From the results in the present study, some inferences may be drawn with respect to lateralization of a brain lesion through analysis of the Wechsler-Bellevue subtest pattern. These inferences, however, would be valid only if one has established through other means that brain damage is present and that the patients are not substantially different from those used in this study. The apparent consistency of these independent findings and Birren's[1] and Cohen's[2] factor analyses lend increased emphasis to the question of the validity of using the Wechsler-Bellevue full scale I.Q. as a measure of psychometric intelligence in brain damaged patients, particularly if patients with lateralized lesions are involved.

In 1954, Blum[11] reported a study of the reliability of electroencephalographic interpretations. He found rather low reliability between interpretations by 5 competent neurologists. Since we have used the electroencephalogram as basis for composing our groups, it should be mentioned that all electroencephalograms used in this study were interpreted or approved by a single electroencephalographer. This, of course, does not increase the validity of the interpretations but should contribute to increased reliability.

SUMMARY AND CONCLUSION

Electroencephalographic criteria were used to divide 185 patients, all brain damaged, into 4 groups. Patients with electroencephalographic disturbances maximized over right hemisphere showed a loss on the Wechsler-Bellevue performance scale, and patients with left sided electroencephalograms showed a loss on the verbal scale. Patients with generalized or normal electroencephalograms showed no difference between the verbal and performance scales, but the group with normal electroencephalograms showed an absolute level superior to the other groups. Halstead's impairment index fell in the range characteristic of brain damage for all groups but failed to show any significant intergroup differences. The question of whether this may be considered a reflection of greater sensitivity of the impairment index to brain damage as compared with the electroencephalogram is raised.

From the findings in this study, it appears justified to assume that lowered scores on the verbal subtests of the Wechsler-Bellevue scale may be associated with dysfunction of the left hemisphere, whereas lowered scores on the performance subtests may be associated with dysfunction of the right hemisphere. No striking differences between verbal and performance subtests appear commonly in patients with generalized brain damage. The criteria for composing our groups and the characteristics of our patients emphasize the importance of imposing appropriate limitations on generalization of the results.

The electroencephalograms were interpreted by Philip T. White, M.D.

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Causes of polyuria and polydipsia in patients with injuries of the cervical spinal cord

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SINCE THE CLASSIC study of Goltz and Ewald,[1] the effects of injuries of the spinal cord upon sensorimotor functions have been written about extensively, but much less has been written about the effect of such injuries on visceral functions that are subserved by the autonomic nervous system.

That transection of the spinal cord deprives segments below the point of injury of suprasegmental control of sensory and motor functions is well known, but the isolated portion of the spinal cord develops increased reflex activities in these functions below the point of injury. In a similar manner, it is generally well known that spinal cord transection is followed by continuous and autonomous functioning of almost all of the structures innervated by the autonomic nervous system. Just as in the case of sensorimotor functions, in the visceral sphere we find evidence of reflex activity. This activity helps to maintain function in the viscera in such a state as not only to permit life to go on but also to permit most physiologic functions such as digestion, renal activity, circulation, parturition, and so on.

For several years, our group, under the direction of Dr. L. J. Pollock, has had the opportunity to study large numbers of veterans who have sustained injuries to the spinal cord. We have been interested in the effects of such injuries on autonomic functions[2] such as sweat secretion,[3] blood pressure regulations,[2,4] glucose metabolism,[4] water metabolism,[4] heat regulation,[4] and gastrointestinal function.[5] These studies have disclosed departures from functions in healthy individuals, which, as might be expected, are most marked in cases of cervical cord injury. Some appear to be explained by the absence of regulatory impulses that would normally descend in the spinal cord from higher levels, such as the diencephalon, thereby producing, below the level of the lesion, hyperreflexia of the sympathetics comparable to the increase in deep tendon reflexes with upper motor neuron lesions. Thus central sweating, that is, sweating induced by increase in the temperature of ambient air, does not occur in the skin that receives its innervation from the spinal cord below the point of injury. This is explained by the fact that descending impulses cannot reach the neurons of origin of the thoracolumbar system, which innervate the sweat glands. However, reflex sweating is unduly profuse below the level of the lesion when induced by such stimuli as distension of the bowel or bladder or by muscular spasms in the voluntary muscles of the bladder.

The present communication is concerned with the effects of injury to the cervical portion of the spinal cord upon water metabolism. The effects of such injury will be described, and a possible explanation for them will be explored.

Our material consisted of 59 patients who had sustained injuries to the cervical portion of the spinal cord, either by penetration of the spinal canal by projectiles or by closed injuries resulting in fracture-dislocations of the cervical spine. In all cases, at least six months

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had elapsed since the time of injury, so that acute shock effects had completely disappeared. None of the patients had shown any evidence of disturbances in water metabolism prior to injury, and all had been in excellent health at the time of injury. In 30 instances, the injury resulted in a complete interruption of functions; in 29, the lesion produced an incomplete interruption of function. Intake of water and output of urine was measured in all 59 patients over a period of several days at different times of the year. In another 3 patients with injuries to the cervical cord, the effect of intramuscular injection of Pitressin in oil on water metabolism was studied.

In healthy persons, the amount of urine excreted in a twenty-four-hour period varies from 1,000 to 1,800 cc. and a comparable amount of water is ingested. Of our 59 patients, 53 excreted over 3,000 cc. of urine daily and 40 excreted over 4,000 cc. of urine daily during the period of observation. Especially noteworthy were the patients who passed huge amounts of urine, such as over 12,350 cc. in 1, over 10,000 cc. in 3, 8,000 to 10,000 cc. in 2, and 6,000 to 8,000 in 10. The amounts of fluid ingested by these patients beyond that found in their food was substantially the same as the urinary volume. Over 4,000 cc. of fluid daily was ingested by 43 of the 59 patients, and, in 8 patients, over 8,000 cc. was ingested per day. It is apparent, therefore, that, among patients with injuries to the cervical portion of the spinal cord, a polyuria of substantial proportions is present in the majority and that this condition is correlated with a marked polydipsia.

The significance of the polyuria and polydipsia in our patients remains to be elucidated. The literature on water metabolism is somewhat contradictory and, in certain aspects, too voluminous to be appropriately discussed in this communication. Physiologists and physicians have studied this subject from diverse points of view, and emphasis has been laid on single aspects of the subject with neglect of others. Here we may consider water metabolism from the following points of view: [1] sweating and water metabolism; [2] water intake or the thirst mechanism; [3] relation of the vagus to water metabolism; [4] relation of the nervous system to renal function; [5] diabetes insipidus; and [6] relation of the spinal cord to water metabolism.

The first avenue of exploration to explain our findings is related to the fact that sweat secretion is disturbed in these patients. They lack the ability to sweat in response to an increased temperature in ambient air, but reflex sweating does occur below the level of the lesion and, at times, may be increased for short periods in response to an appropriate stimulus, such as a distended bladder or muscular spasm below the level of the lesion. The question may be asked whether the polyuria we observe is a compensation for a lack of sweating.

In persons who have been subjected to total sympathectomy, Ray,[6] like others, has found a loss of sweating and an associated marked intolerance to heat, but, in his patients, he did not find polyuria or polydipsia. A disturbance in sympathetic innervation of the sweat glands, therefore, does not seem adequate to account for the polyuria and polydipsia observed in our patients.

The mechanism of thirst that is the indicator of water deficiency is still controversial. Claude Bernard[7] suggested that this sensation is chemically mediated with dehydration, producing changes in the osmotic state of the blood. These changes act as a stimulus to some nerve center, possibly the hypothalamus, within the central nervous system from which impulses originate that result in the drinking of water. He and, many years later, Adolph[8] showed that, when a state of dehydration existed, an animal with an esophageal fistula would continue to drink enormous amounts of water, up to 70 liters a day, which failed to quench thirst, even though the pharynx is kept moist. Dill[9] points out that increasing osmotic pressure of the blood by injection of NaCl is much more effective to produce thirst than is an injection of an equivalent amount of urea.

W. B. Cannon[10] has offered an opposing theory, according to which the essential stimulus for thirst occurs because of drying of the mucous membrane of the mouth and throat. Dehydration, he believes, produces a reduction in salivary secretion, which, in turn, causes the dryness that is the subjective stimulus for thirst. Bellows and von Wagenen,[11] however,

showed that denervation of the mouth and throat, so that afferent impulses could not reach the brain, did not affect the intake of water. Steggerda[12] tells of a man lacking active salivary glands who found it necessary to drink frequently in order that his mouth might be kept comfortably moist. He took such small amounts of water each time, however, that his total daily intake was not increased above the normal.

Finally, Montgomery[13] adduced evidence against the view of Cannon when he showed that resection of the salivary glands in dogs did not induce polydipsia. The thirst seen in our patients was obviously not due to either decreased moisture in the pharynx or an abnormality in the nerve center upon which osmotic changes in the blood act to initiate drinking. The mechanism for their polydipsia may be that suggested by Barker, Adolph, and Keller[14] when they point out that neither thirst nor polyuria is primary in experimental diabetes insipidus. In the healthy dog, they state, the development of dehydration may be compensated for either by increased concentration of the urine or by a greater intake of fluids, but, in the animal with diabetes insipidus, only a polydipsia can compensate for a hydropenia, since the kidney is apparently unable to excrete a more concentrated urine.

We should discuss the role of the vagal system in water metabolism since, in our patients, afferent and efferent communication via the vagi remains between the brain stem and the viscera. Literature on this subject indicates that the effect of the vagal system on water metabolism is negligible. Towbin[15] reports that bilateral vagotomy in dogs produces only a slight increase in the amount of water ingested. Dragsted,[16] who has performed many double vagotomies in man, reports that there is neither polyuria nor polydipsia following this procedure.

It is particularly pertinent in the present thesis to examine the factor of regulation of renal function by the nervous system. As early as 1859, Claude Bernard[17] showed that cutting the splanchnic nerve increased the flow of urine from the homolateral kidney. Marshall and Kolls[18–20] also studied the effect of the complete denervation of the kidney and found that this procedure resulted in a marked increase in the output of water, chlorides, and carbonates by the kidney for a period of months. Urea, phosphate, and sulfates were also excreted in greater than normal amounts but not as great as water, chlorides, and carbonates. Under these conditions, creatinine, ammonia, and phenolsulfonphthalein are not excreted in increased amounts. The denervation, they believe, increases glomerular filtration and also decreases tubular reabsorption of water and salt. Because partial occlusion of the renal artery was found to have effects exactly opposite to those of splanchnotomy, Marshall and Kolls[21] believe that the latter procedure acts entirely by increasing blood flow through the kidney.

Donnet and Pruneyre[22] also report that splanchnic nerve section produces a diuresis within twenty-four hours and that it persists for twenty days to four months. They say that the urinary constituents, under these circumstances, are not changed in concentration. They also state that combined splanchnic resection and removal of the lumbar sympathetic chain produces less polyuria than splanchnic resection alone. Furthermore, they report that the denervated kidney is very sensitive to the antidiuretic effects of posterior hypophyseal extracts. According to these authors, the action of the nervous system is a specific one on renal excretion and is not a simple vasomotor effect. Kaplan and Rapoport[23] contend, from their study of the effect of splanchnicotomy on urinary excretion of sodium and chloride, that the load of these constituents in the urine is controlled by the splanchnic nerves via the renal tubules and not on a vascular basis.

Finally, denervation of the kidneys in dogs is reported by Caldwell, Marx, and Rowntree[24] to produce a polyuria and polydipsia which persist for two months. After five months, they say, the only evidence of increased function in their dogs is an increase in the normal diuresis which follows the ingestion of water. From such evidence as adduced above, it is not difficult to postulate that transection of the spinal cord in the cervical region precludes the downward passage of regulatory impulses from above and may well produce a polyuria and polydipsia by depriving the kidney of normal regulatory neural control.

There is evidence to show that pituitrin is capable of acting on the isolated kidney to produce antidiuresis from the cross circulation experiments by Verney and his associates,[25–27] and, therefore, it is not surprising that Janssen[28] found transection of the cervical spinal cord or the brain stem at the colliculi did not alter the antidiuretic effects of Pituitrin on the kidney in diabetes insipidus. This merely proves that extracts of the pituitary gland can, like many drugs, act on the kidney itself. In our patients with polyuria and polydipsia, the mechanism by which an adequate amount of antidiuretic hormone is produced has not been altered. Is it possible that this hormone is not capable of acting because of injury to the cervical portion of the spinal cord? This is doubtful and was proven not to be the case in observations we made on the effects of Pitressin injected into 3 patients with lesions of the cervical cord.

In each of these patients, the twenty-four-hour intake and output were measured as a control on the days before and after the experiment. On the day of the experiment, 0.5 cc. of Pitressin tannate in oil was injected at 7:30 A.M. The urinary output in the first case dropped from the control 6,550 to 972 cc., going back the next day to 6,100; in the second case, from 7,975 to 1,340 cc. and back to 7,250 the following day; and, in the third patient, 7,358 to 925 cc. and back to 8,695. In all 3 patients, there was comparable, though not as marked, reduction in fluid intake. The antidiuretic effect of the injected Pitressin was most marked very shortly after injection in all instances and then gradually decreased. It is clear, therefore, that, in our patients, the diabetes insipidus syndrome is not due to an inability of the kidney to respond to antidiuretic pituitary extract.

Since our patients presented changes in water metabolism similar to diabetes insipidus, a condition in which large amounts of dilute urine are excreted and polydipsia is associated, it is appropriate to examine the neural aspects of this condition. A good deal of controversy has raged as to the site of injury or disease from which the syndrome of diabetes insipidus originates. Frank[29,30] ascribed the disease to a lesion of the posterior lobe of the hypophysis producing hypersection of a diuretic principle. Simmonds,[31,32] Goldzieher,[33] von Gierke,[34] Maranon,[35] and Zadek[36] also attributed this syndrome to a lesion of the posterior lobe of the pituitary but regarded it as due to a deficiency of secretion. The hypothalamus was considered the site of the lesion responsible for diabetes insipidus by Leschke and Schneider;[37] Bailey and Bremer;[38] Camus, Roussy, and LeGrand;[39] Aschner;[40] Houssay;[41] and others. Biggart[42] studied 700 brains, and, in 7 instances, clinical diabetes insipidus was associated with lesions in the supraoptic nucleus of the hypothalamus, the supraoptic hypophyseal tract, or the posterior lobe of the hypophysis.

At the present time, the views of Fisher, Ingram, and Ranson[43] based on focal destructive lesions placed in cats' brains by a stereotaxic instrument have gained considerable acceptance. These authors claim to have shown that a lesion in the supraoptic nucleus of the hypothalamus, the posterior hypophysis, or the nerve tract connecting these 2 structures (the supraoptic-hypophyseal tract) will produce diabetes insipidus because they all cause a decreased secretion of the antidiuretic hormone from the posterior lobe of the pituitary gland. These authors showed that section of that tract alone without damage to either the supraoptic nucleus or the posterior hypophysis will be followed by atrophy of the cells in the nucleus and in the neural lobe of the pituitary.

Elucidation of this portion of the mechanism for the production of diabetes insipidus still does not clarify the manner in which this system functions in the intact animal nor the way in which the antidiuretic hormone functions once it is released. Having already produced a state of diabetes insipidus by damage to the hypothalamic-hypophyseal mechanism, destructive experiments performed on the nervous system below the level should not and does not alter the existing state of polyuria and polydipsia. This was shown by Bourguin[44] who sectioned the spinal cord with and without double vagotomy, by Houssay and Carulla[45] who denervated the kidneys, and by Rubio[46] who sectioned the greater and lesser splanchnic nerves, removed both sympathetic chains, and performed double vagotomy without affecting experimentally produced diabetes insipidus.

It is fallacious to conclude from these experiments that the exclusion of descending regulatory impulses is not part of the mechanism responsible for the production of diabetes insipidus. When the radial nerve is cut in the upper arm, subsequent sectioning of the nerve below the point of injury will not alter the sensory defect already produced in the hand or motor defects in the dorsiflexors of the wrist and fingers, because no further interference with the passage of neural impulses into or out of the central nervous system can be induced that is not already there. As Miller[47] points out, "Pituitrin may possess an almost specific and direct major influence on the hypothalamus, engendering in this structure impulses for water regulation which are transmitted to the body by hypothalamic efferent pathways." We believe that the exclusion of regulatory impulses from the hypothalamus passing downward in the spinal cord and then out to the periphery by the sympathetic system is still vital in producing the polyuria and polydipsia.

In our patients with injuries to the cervical spinal cord, the hypothalamus and hypophyseal systems remain intact, so that hormonal secretion can go on unimpaired by the hypophysis and neural intercommunication between these 2 structures is normal. Yet we have found a marked polyuria and polydipsia. The conclusion forces itself upon us, then, that the mechanism for this state can only be explained by the failure of regulatory neural impulses to pass down past the point of injury from their point of origin in the hypothalamus. This mechanism is precisely similar to the process involved in heat regulation, in which the brain is activated by the temperature of the circulating blood. Thus, in 1924, Sherrington[48] showed that, after low cervical cord section, immersion in ice of the hind quarters of a dog caused shivering in the unparalyzed anterior leg muscles. A warming of the carotid blood was shown by Moorhouse[49] to cause peripheral vasodilation and hyperventilation. In fact, Ranson[50] and his associates found that local heating of the hypothalamus by a high frequency alternating electric current stimulated the heat loss mechanism to produce panting and sweating.

There is a striking paucity of reports on the effect of lesions in the spinal cord on water metabolism. Neither Goltz and Ewald[1] nor Popoff,[51] who studied the effects of destruction of the spinal cord in dogs, made any mention of disturbance in this function. Herrmann, Morin, and Vial,[52] however, studied urinary output in dogs that were observed as long as four hundred eighteen days after destruction of the spinal cord below the cervical region. These animals, after a period of eight to twelve days during which urinary output was decreased, showed a marked polyuria and polydipsia which persisted for two to eight weeks. Following this period, the dogs entered an indefinitely long stage, during which there was a lesser but definite degree of polyuria and polydipsia. Interestingly, these authors found that prior section of the vagi did not influence the development of these 3 stages. A final point they noted is that their animals secreted greater amounts of urine at night than during the day, a reversal of the normal pattern. The findings in our patients are in agreement with the findings of Herrmann, Morin, and Vial, and, like these authors, we believe that disturbances in water metabolism are due to the fact that regulatory impulses from higher levels in the nervous system, such as the diencephalon, cannot descend to the points of origin of neurons concerned in the regulation of water metabolism.

SUMMARY AND CONCLUSIONS

Study of water metabolism in 59 patients with injuries to the cervical portion of the spinal cord shows that the great majority of them excreted abnormal amounts of fluids. The polyuria and polydipsia observed were found, in 3 patients studied, to be reduced markedly in degree by the intramuscular injection of Pitressin in oil. Because the hypothalamic-hypophyseal system is intact in our patients and because pituitrin is demonstrated to be capable of producing antidiuresis in our subjects, it is concluded that interruption at the cervical level of neural pathways which are concerned in water metabolism in the intact organism is responsible for a diabetes insipidus-like syndrome. This suggests that the exclusion of descending impulses from the hypothalamus to lower centers in the spinal cord are important in producing diabetes insipidus.

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Neurology

BOOK REVIEWS

Mental Subnormality: Biological, Psychological and Cultural Factors

by Richard L. Masland, Seymour B. Sarason, and Thomas Gladwin, 442 pp., ill., Basic Books, Inc., New York, 1958. $6.75

This volume, published under the auspices of the National Association for Retarded Children, points out the serious nature of the problem of mental subnormality. An increasing proportion of patients, especially in centers for children, suffer from disease or damage to the nervous system. This is due to the increasing skill with which ordinary illness is handled and the prolonged life span of the brain-injured child.

A survey to review the present status of the problem so as to provide a sound basis on which to develop a program of research was the basis for this volume. Two broad areas were reviewed: the factors which produce anatomic and chemical abnormalities and the cultural and environmental factors.

Part one, prepared by Dr. Richard Masland, deals with prevention of subnormality. His aim was to indicate the areas of research which were relevant, to summarize knowledge in each of these areas, and to point out new areas or new approaches which might be successful. He succeeds very well.

Part two, by Seymour B. Sarason and Thomas Gladwin, deals with the psychologic and cultural problems in mental subnormality. They attempted to present the problem in terms that will encourage social scientists to view mental subnormality as an important area of research. With expanding knowledge of the subnormal will come a better understanding of the normal.

For anyone interested in mental retardation, cerebral palsy, or epilepsy, this volume will provide an excellent basis for study and research. The whole thing is well done and timely and is to be recommended highly.

J. P. R.

Biochemistry and the Central Nervous System

(Second Edition). Henry McIlwain, 288 pp., 1959, Little, Brown and Co., Boston.

The first edition of this book appeared in 1955. The author notes that great advances have occurred in the interval, and that about one-quarter of the present edition consists of new material and a similar percentage of the references cited have been published in this period.

The author has done a skillful job of revision and inclusion of additional material without changing the convenient size of the volume. The book is highly readable and contains a wealth of information presented in a well-organized, succinct style. The text is augmented by good illustrative data in the tables and figures.

The 14 chapters are supplemented by full bibliographies and comprehensive author and subject indexes. The subject matter is restricted to the central nervous system. Peripheral

nerves, ganglia, sensory receptors, neuromuscular junctions, and muscles are not treated in detail. The emphasis is upon the normal; good examples of disordered metabolism and function are cited but do not constitute the main theme. The foregoing must not be construed as a criticism but as an indication of the author's intentions to restrict himself to his stated subject.

This is an authoritative work. The laboratory which the author directs has worked on and made significant contributions to almost every subject discussed. The author has a broad background in the historic aspects, in chemotherapy of the nervous system, and in the whole discipline of neurochemistry.

It is perhaps unfair, in view of the uniform excellence of the book, to single out chapters for emphasis, but the reviewer found "Vitamins and the Central Nervous System" and "Chemical and Enzymatic Make-Up during Development" particularly rewarding.

The conclusion of the last chapter, which considers the speed of chemical change in the brain, should be required reading for all neurologic scientists. This book presupposes a fair background in biochemistry and represents a most valuable reference work for neurochemists. Nevertheless, in the opinion of this reviewer, the book also constitutes the best reference work available for all other neurologic scientists as well.

D. B. T.

J. M. Charcot 1825-1893: His Life—His Work

by Georges Guillain, edited and translated by Pearce Bailey, 202 pp., Paul B. Hoeber, Inc., New York, 1959.

Jean-Martin Charcot was the founder of the French school of neurology and was one of the most important figures in the history of neurology as a specialty. He occupied the first professorial chair of clinical neurology at the Faculty of Medicine in Paris. A definitive biography of Charcot is long overdue. All students of neurology and of the history of medicine are indebted to Professor Georges Guillain, now Professor Emeritus and former holder of Charcot's chair at the Faculty of Medicine in Paris, for writing this biography, and to Dr. Pearce Bailey for editing and translating it and making it available in English.

This book, as Dr. Bailey says in his preface, deals with two celebrated French monuments: one a man, Charcot; the other a medical institution, the Salpetrière. These two are inseparable, for without one there would not be the other in the sense that we understand both of them today. The author of a true life of Charcot must include the story of the Salpetrière, which Guillain has done in this biographic sketch.

This monograph is divided into two parts. The first is devoted to the life of Charcot, his personality, his relationship to the Salpetrière, and his pupils, who have been the outstanding leaders in French neurology. It is a study of the man, his working habits, and his literary, artistic, and philosophic accomplishments. The second part is devoted to Charcot's scientific works and discoveries.

Charcot was a clinician to whom patients flocked from almost every part of the world. There are few conditions in neurology that were not investigated by him. His descriptions of amyotrophic lateral sclerosis, multiple sclerosis, Charcot-Marie-Tooth disease, and the tabetic arthropathies are of paramount interest to neurologists. Some of his other interests, especially those related to hysteria, the neuroses, and hypnotism, and the work on faith healing he was doing at the time of his death, are somewhat more controversial, but these, too, are important. One must recall that Charcot had a profound influence on Freud and on the development of psychoanalysis. It was through his conceptions of psychologic processes that some of his successors were able to develop theories of the neuroses which were acceptable to science.

This small book is beautifully printed and bound. It contains a glossary which helps the reader to understand special aspects of training in French academic medicine and of hospital and medical school appointments. It is a most important contribution and will be read eagerly by all who are interested in the study of human personality and in the development and evolution of medical science, especially that aspect of medicine which deals with the nervous system.

R. N. D.

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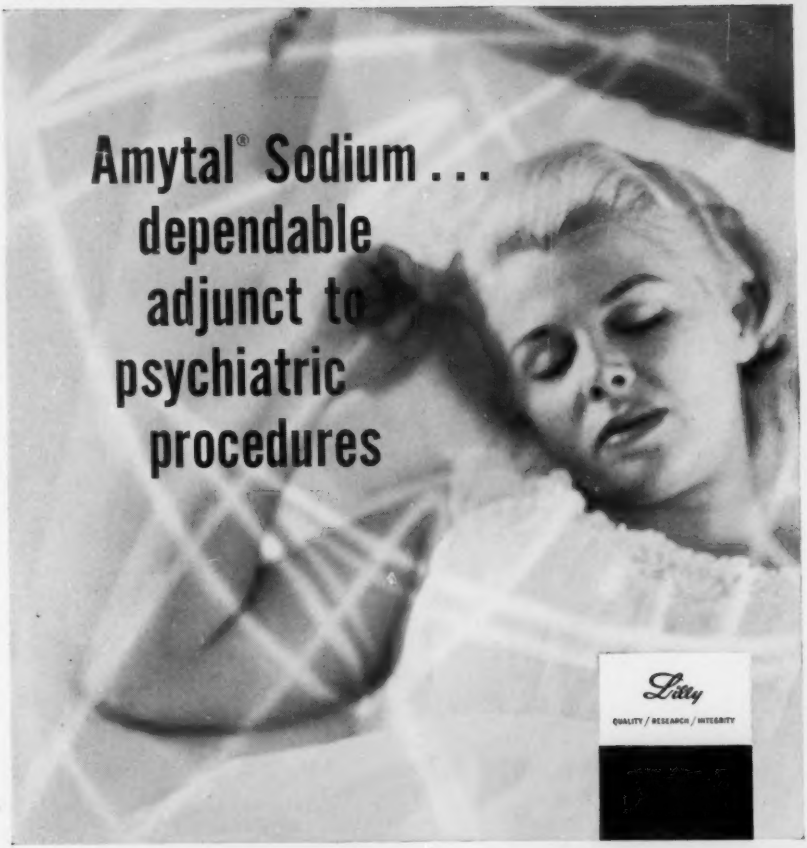

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1. Ehrmantraut, W., et al.: Scientific Exhibit Presented at the District of Columbia Medical Society Meeting, Nov. 24, 1958, Washington, D.C.

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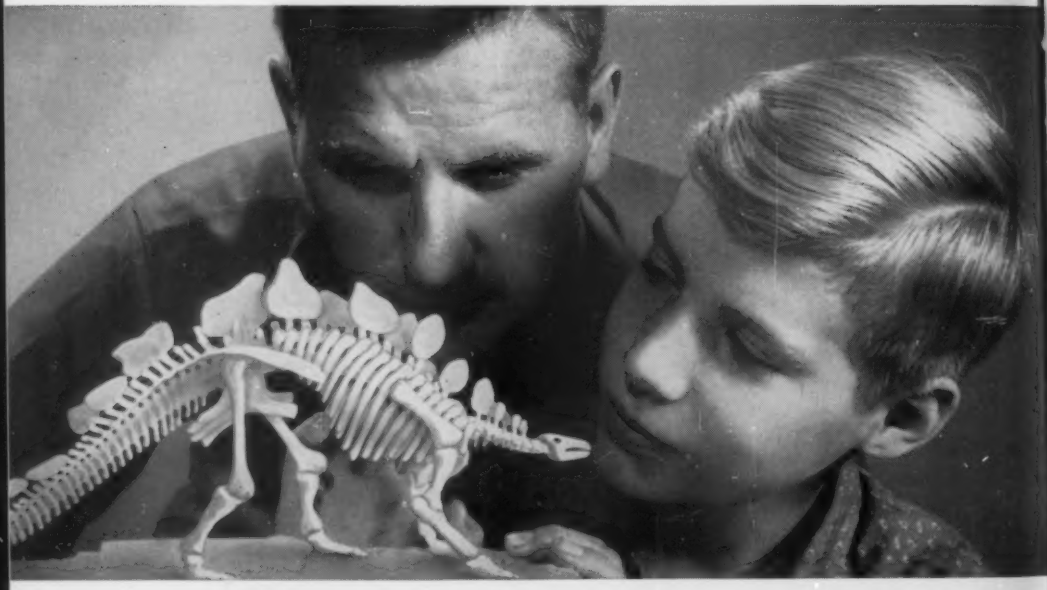

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references: 1. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. 2. Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* 116:71 (July) 1959. 4. Arnow, L. E.: Phenelzine: A Therapeutic Agent for Mental Depression, *Clinical Med.*, 6:1573 (Sept.) 1959. 5. Dickel, H. A.; Dixon, H. H.; Shanklin, J. C., and Dixon, H. H., Jr.: Tension Fatigue States and Their Adjunctive Treatment Using Nardil, *Clinical Med.*, 6:1579 (Sept.) 1959.

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		"good"			
Lewis[3]	38	25	6	—	7
O'Doherty & Shields[4]	17	"excellent" 14	2	1	0
		"significant"			
Park[5]	30	27	—	2	1
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REFERENCES: 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Lewis, W. B.: California Med. 90:26, 1959. 4. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 5. Park, H. W.: J.A.M.A. 167:168, 1958. 6. Plumb, C. S.: Journal-Lancet 78:531, 1958.

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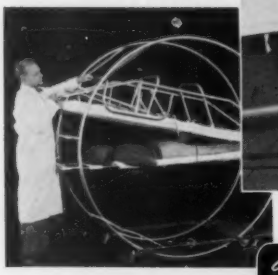

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1. Brock, S., Mod.: Bull. New York Acad. Med. *32*:202, 1956.
2. Doshay, L. J.: Parkinsonism and Its Treatment, Philadelphia, J. B. Lippincott, 1954, pp. 87-88.
3. Doshay, L. J., Constable, K., and Zier, A.: Neurology *3*:360, 1953.

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DECEMBER 1959

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Annual AAN Meeting To Be Held in Miami The twelfth annual meeting of the American Academy of Neurology will be held at the Eden Roc Hotel in Miami Beach, Fla. (April 25-30, 1960). As previously announced, the deadline for the receipt of abstracts of papers-from-platform and of scientific exhibits is Tuesday, December 1, 1959. The former, to consist of no more than 150 words, should be sent to Dr. Joseph M. Foley, Seton Hall College of Medicine, Jersey City 4, N.J.; the latter, also to contain no more than 150 words, should be sent to Dr. Richard D. Walter, University of California Medical Center, Los Angeles 25, Calif.... Additional information on the Academy's 1960 annual meeting will appear in forthcoming issues of the Newsletter.

AAN Review Courses Enlarged for the Miami Meeting Anticipating a large attendance at the AAN annual meeting in Miami Beach, the Academy's Special Courses Committee (A. B. Baker, chairman) has enlarged the number of review courses to be offered to Academy members and their guests at the Eden Roc Hotel, Miami Beach (April 25-27, 1960). Among the new courses to be offered are: child neurology (Paul Ellwood, chairman); central nervous system infections (Charles A. Kane, chairman); genetics in neurology (Leonard T. Kurland, chairman); and the neurologic aspects of internal disease (Gilbert H. Glaser, chairman). Among the courses to be repeated are: neuropathology (Erland R. Nelson, chairman); neurochemistry (Maynard Cohen and D. B. Tower, chairmen); electroencephalography (Frank Morrell, chairman); language disorders (Joe R. Brown, chairman); and neuro-ophthalmology (Nathan S. Schlezinger, chairman)....The registration fees for all courses except neuropathology are: $10 for Junior members; $15 for Fellows, Actives, and Associates; and $30 for nonmembers. The registration fee for neuropathology is $15 for Junior members; $20 for Fellows, Actives, and Associates; and $20 for nonmembers. The extra fee for neuropathology is for the loan to each registrant of a box of 100 microscopic slides for study before and during the course....Early registration in these courses is urged; no applications will be received after April 1, 1960. Applications should be sent to Mrs. J. C. McKinley, Executive Secretary, American Academy of Neurology, 4307 East 50th Street, Minneapolis 17, Minn.

Philadelphia Neurological Celebrates Seventy-fifth Anniversary

On October 23, 1959, the Philadelphia Neurological Society celebrated its seventy-fifth anniversary at the Barclay Hotel, Philadelphia. The commemorative program featured a scientific session in the afternoon, followed by cocktails and dinner. Highlighted in the scientific program were addresses by Bernard J. Alpers on "Contribution of Philadelphia Neurologists to Clinical Neurology" and by Roland P. Mackay on the "Future of Neurology."

Million Dollar Donation Goes to the MGH

The Joseph P. Kennedy, Jr., Memorial Foundation (named for a Naval aviator son who was killed in World War II) has announced a $1,000,000 donation to the Massachusetts General Hospital for the establishment and maintenance of a laboratory for research in diseases of the nervous system of infants and children. The principal neurologic conditions to be studied, under the terms of the donation, are mental retardation, cerebral palsy, and epilepsy. The program will be under the professional direction of Raymond D. Adams....The recent donation to MGH represents one of the many contributions (at least $12,000,000) to medical research by Boston multi-millionaire, Joseph P. Kennedy, one-time (1937-40) ambassador to the Court of St. James.

WFN Commission of Neurochemistry Meets in Antwerp

The Commission on Neurochemistry of the World Federation of Neurology held its first organizational meeting in Antwerp, September 29 and 30, 1959. Here the members of the Commission, blueprinted plans for the establishment of a permanent secretariat as part of the WFN Secretariat in Antwerp; made plans for the organization of a registry of neurochemical material; and planned for the conduct of a symposium in neurochemistry during the Seventh International Neurological Congress, to be held in Rome in 1961. The major topics to be covered in the proposed symposium are the lipids and lipoproteins and their metabolism and disorders of myelin....Dr. A. Lowenthal of Antwerp's Institut Bunge was elected secretary of the Commission. All communications related to the work and programs of the Commission should be addressed to Dr. Lowenthal who, in turn, will inform medical and scientific journals of the activities of the Commission....The WFN Commission of Neurochemistry is one of several problem commissions already organized within the WFN to better the exchange of world information in specialized fields and to study, through the pooling of international talent, problems which are susceptible to collaborative research.

---

[1]Bauer (Hamburg), Brante (Eskilstuna, Sweden), Cumings (London), Edgar (Amsterdam), Folch-Pi (Waverley, Mass., U.S.A.), Korey (New York), Lowenthal (Antwerp), Pearse (London), Quastel (Montreal), Richter (Cardiff, England), Svennerholm (Göteborg, Sweden), and Tourtelotte (Ann Arbor, Mich., U.S.A.) Others present as observers were Ludo van Bogaert, President of the WFN and Charles M. Poser, WFN Medical Executive Officer.

First Argentine Congress Held in Buenos Aires

The Argentine Neurological Society (Sociedad Neurologica Argentina), an affiliate of the World Federation of Neurology, organized the First Argentine Neurological Congress in the Alvear Palace Hotel, Buenos Aires (November 5-7). The scientific program, drawn up by Argentine neurologists and neurosurgeons, included discussions of the neurologic aspects of collagen diseases, the pathophysiology of the myoneural junction, the neuralgias, peripheral nerve tumors, and metabolic neuropathies. At the congress were distinguished visiting neurologists from Uruguay, Brazil, Chile, Peru, Bolivia, Paraguay, and other countries. This congress, in the words of its president may well serve as a precursor of future inter-American neurologic congresses to be held every four years between the international neurologic congresses.

Kremlin Medical Chief Visits NIH

Dr. A. M. Markov, Chief of the Kremlin's Medical Service and personal physician to Soviet Premier Nikita Khrushchev, intently inspected the programs and facilities of the National Institutes of Health in Bethesda (September 25, 1959). He was accompanied by Dr. V. N. Butrov, his colleague and interpreter. The distinguished visitors were welcomed by Arthur S. Fleming, Secretary of the Department of Health, Education, and Welfare; Leroy E. Burney, Surgeon General of the Public Health Service; and James A. Shannon, Director of the National Institutes of Health. The Surgeon General's welcome set the tenor: "No nation, seeking better health, takes it from another; and the gains of any nation help everywhere to advance this common cause of mankind," Dr. Burney said....Dr. Markov replied in kind, "The doctors of our two countries can certainly get together and help the health of people throughout the world."

London Conference on Scientific Aspects of Mental Deficiency

Arthur W. Pense, Deputy Commissioner, New York State Department of Mental Health, announces that the Second International Conference on the study of mental deficiency will be held in London (July 24-29, 1960). The Conference, organized and sponsored by the American Association of Mental Deficiency and the Royal Medico-Psychological Association, will be conducted in cooperation with the British National Association for Mental Health. The scientific program, open to professional workers, will consider the latest medical, psychologic, social, educational, and administrative developments in this field. The London conference will precede the meetings of the World Federation for Mental Health to be held in Edinburgh (August 7-12, 1960). Plans are being made for visits to residential facilities and training centers in England between the ending of the London Conference and the opening of the Edinburgh meetings....For further

information, write to Harvey A. Stevens, Chairman, AAMD, Committee on International Conferences on Mental Deficiency, 301 Troy Drive, Madison 4, Wis.

Board Certifies 10 Diplomates in Neurology The American Board of Neurology and Psychiatry certified 10 new diplomates in neurology after the examinations held in Chicago (October 19-20, 1959). The new diplomates are: Charles Allen Bonsett (Indianapolis), Norman Gerschwind (Boston), Robert James Joynt (Iowa City), Harold Koenig (Chicago), Eugene W. Loeser, Jr. (Chapel Hill), Cesare T. Lombroso (Boston), Dewey A. Nelson (Wilmington, Del.), Herbert E. Rosenbaum (University City, Mo.), Luis P. Sanchez Longo (Santurce, Puerto Rico), Leslie Tu-lin Ch'eng (Sedro-Wooley, Wash.), and Stephen J. Dutch, Jr. (Omaha).

Epilepsy Group, ARNMD To Meet in New York The American Epilepsy Society and the Association for Research in Nervous and Mental Disease will hold their annual meetings at the Hotel Roosevelt in New York City on December 10, 1959, and December 11 to 12, 1959, respectively. The scientific sessions of the Epilepsy Society include a morning symposium on the basic mechanisms of anticonvulsant drugs, a presidential address by Robert B. Aird, and afternoon sessions on miscellaneous topics. The participants in the morning symposium are: F. B McNaughton, Dixon Woodbury, J. E. Toman, Thomas C. Butler, and H. Houston Merritt, symposium chairman. Included in the afternoon session of miscellaneous topics is: "A Survey of Public Attitudes Toward Epilepsy" by William Caveness and George Gallup, director of the Gallup Poll....The two days following the epilepsy meetings, the Association for Research in Nervous and Mental Disease will open its traditional annual meeting at the Hotel Roosevlt. The subject of the ARNMD meeting is "Mental Retardation"....Among other meetings to be held in New York City around this time are that of the Eastern EEG Society on December 9, at the Lennox Hill Hospital, and the annual meeting and examinations of the American Board of Neurology and Psychiatry at the Neurological Institute of New York on December 13-16, 1959.

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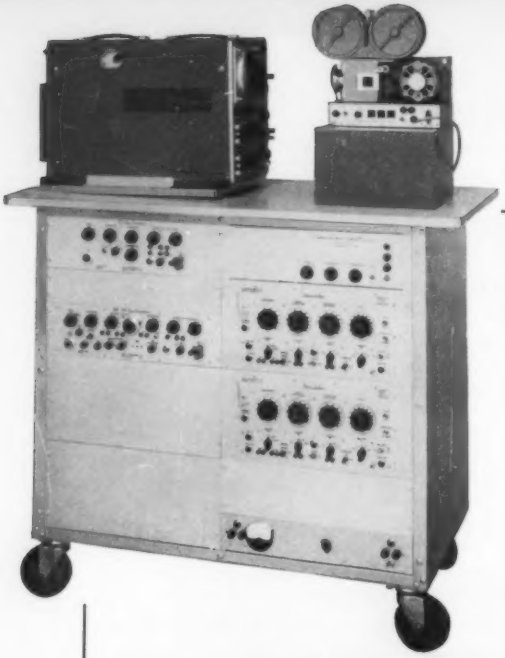

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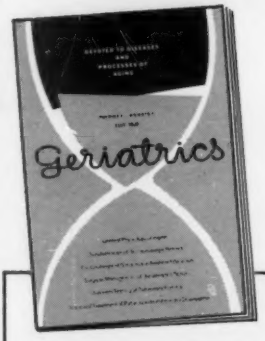

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